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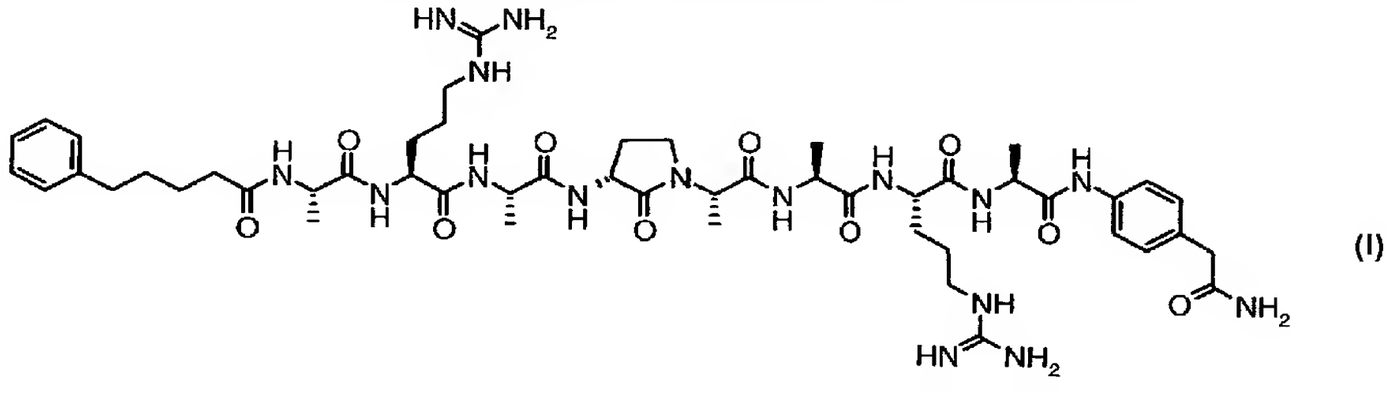
(54) Title: SOLUTION-PHASE PROCESS FOR THE MANUFACTURE OF DECAPEPTIDE



(I)

(57) Abstract: A process for the manufacture of a salt of the compound of formula (I) which process comprises coupling together an appropriate carboxylic acid and amine, wherein the arginine residues are protected by protonation, in particular as the hydrochloride salts. Novel intermediates and processes for their preparation are also described and claimed.

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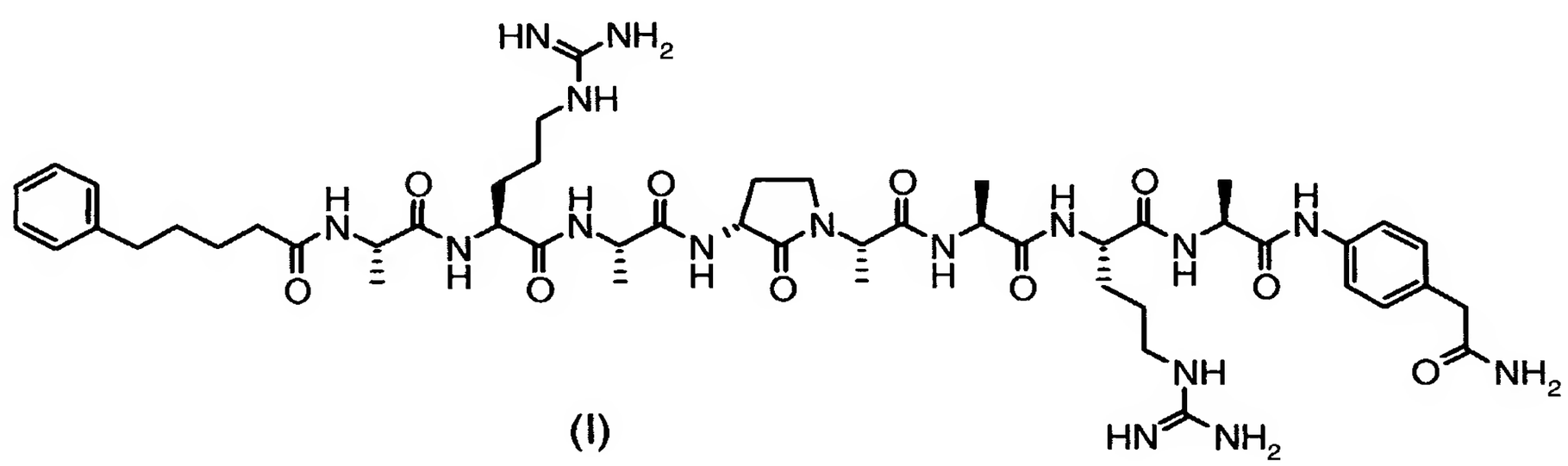
SOLUTION-PHASE PROCESS FOR THE MANUFACTURE OF DECAPEPTIDE

The invention concerns a novel chemical process, and more particularly it concerns a novel chemical process for the manufacture of salts of 5-phenylpentanoyl-(S)-alanyl-(S)-arginyl-(S)-alanyl-{(S)-2-[(R)-3-amino-2-oxopyrrolidin-1-yl]propionyl}-(S)-alanyl-(S)-arginyl-(S)-alanyl-4-aminophenylacetamide of the formula (I).

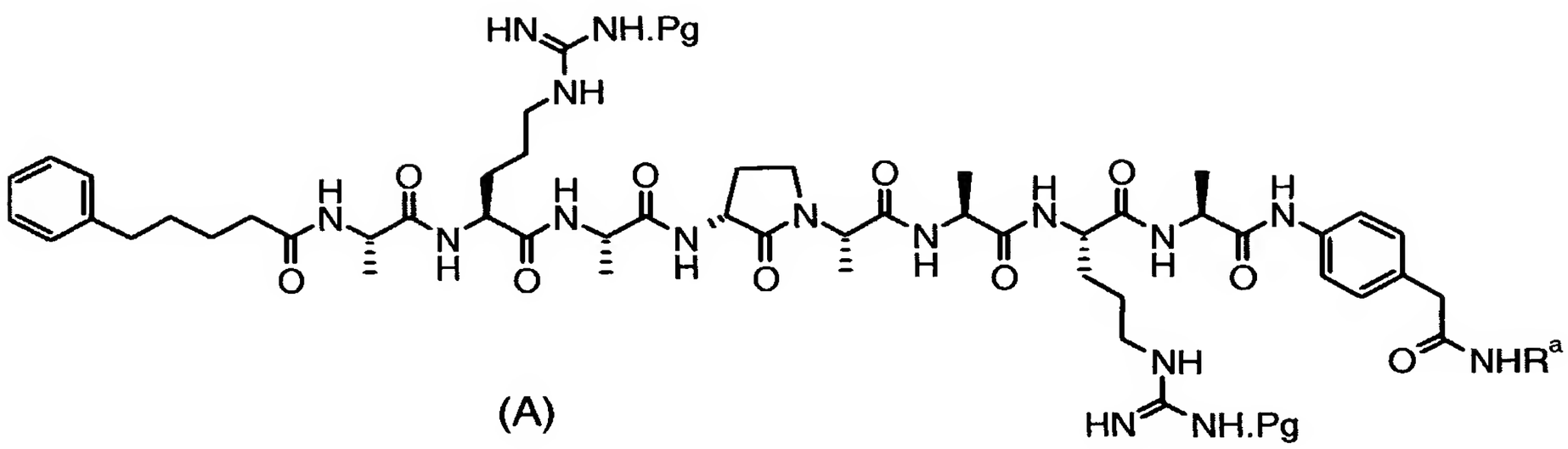


(I)

In this and other formulae shown herein, the absence of a moiety at the end of a bond signifies a methyl group as is conventional.

The pharmaceutically acceptable salts of the compound of formula I are disclosed in International Patent Application, Publication No. WO 97/31023 and possess pharmacologically useful properties for use in treating autoimmune diseases or medical conditions, such as rheumatoid arthritis and other MHC Class II dependent T-cell mediated diseases. WO 97/31023 discloses their preparation using solid phase synthesis, that is using a polymeric support to build up the molecule and subsequent cleavage of the molecule from the support. However the use of solid phase synthesis methodology is inconvenient and difficult when large scale manufacture is required. There is therefore a need to find an alternative procedure which avoids solid phase synthesis and which allows convenient and economic manufacture of the salts in a pure form. It is also particularly desirable for large scale manufacture to find a procedure which involves starting materials and intermediates which allow them to be readily isolated in a pure form and in a good yield.

International Patent Application No PCT/GB01/03228 describes a process for the manufacture of a salt of the compound of formula (I) that does not require solid phase synthesis, and which comprises deprotection of a compound of the formula A or a salt thereof:

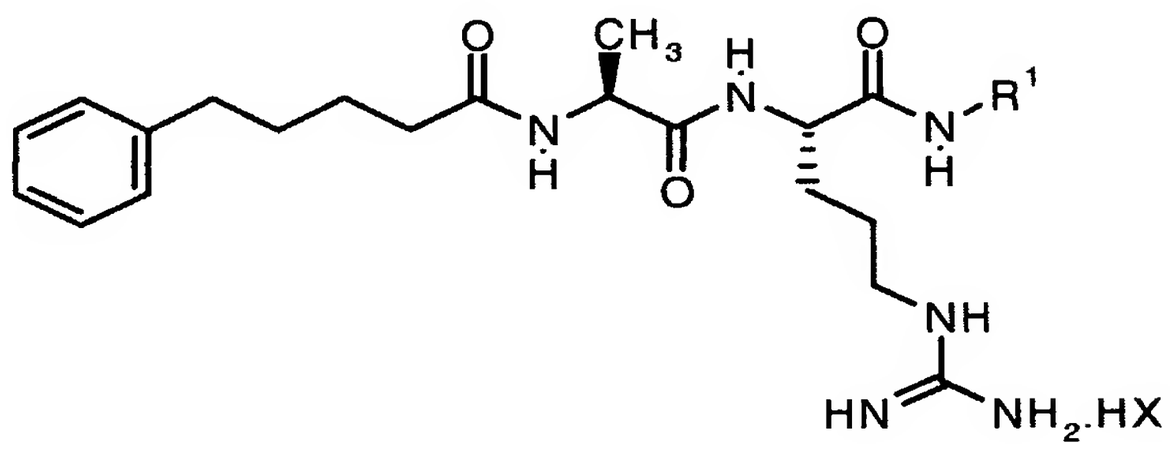


(A)

wherein: groups Pg may be the same or different and are arginine protecting groups, and in particular are nitro; and R^a is hydrogen or a protecting group for an amino group of an acetamide moiety, such as benzyl. Typically deprotection will require an additional process step, for example chemical reduction using catalytic hydrogenation.

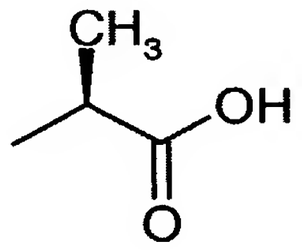
The applicants have found an alternative route to the salts of compounds of formula (I) using a different protecting group, which requires less processing steps.

According to the present invention there is provided a process for the manufacture of a salt of the compound of formula (I) as defined above: which process comprises coupling together a carboxylic acid of formula (II) or a salt thereof:



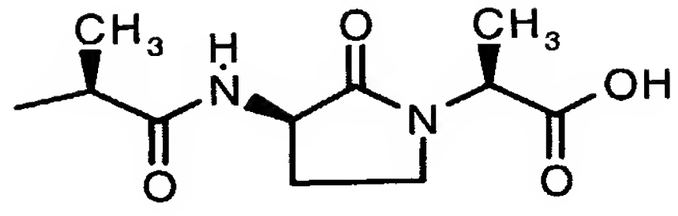
(II)

where X is a anion, and R^1 is either a group of sub-formula (i)



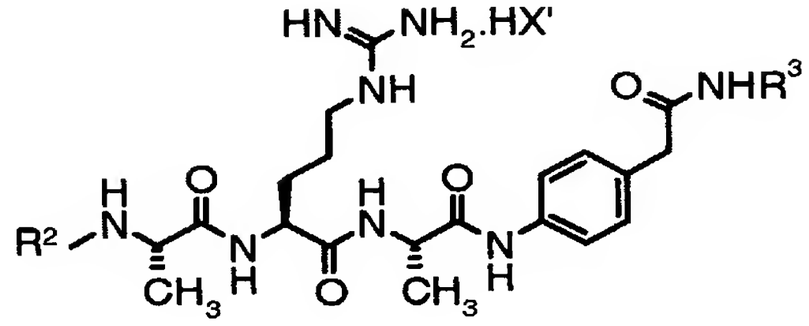
(i)

or a group of sub-formula (ii)



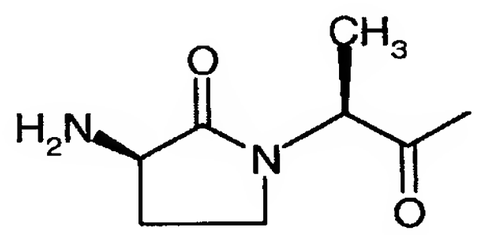
(ii)

with a compound of formula (III)



(III)

wherein X' is an anion, R^3 is hydrogen or a protecting group for an amino group of an acetamide, and R^2 is a group of sub-formula (iii)



(iii)

or hydrogen,

provided that when R^1 is a group of sub-formula (i), R^2 is a group of sub-formula (iii) and where R^1 is a group of sub-formula (ii), R^2 is hydrogen;

and thereafter if desired, converting the resultant acid addition salt to a different salt.

Using the process of the present invention eliminates the need for a separate arginine deprotection step.

Salts obtained by this process may be pharmaceutically acceptable salts. Those which are not pharmaceutically acceptable salts, are nevertheless useful for conversion to pharmaceutically acceptable salts by carrying out a subsequent salt exchange procedure. Such salt exchange procedures are well known in the art. Suitable salt exchange procedures include, for example an ion exchange technique, optionally followed by purification of the resultant product (for example by reverse phase liquid chromatography or reverse osmosis).

Preferably the process is carried out so that the desired pharmaceutically acceptable salt is obtained directly without the need for a subsequent salt exchange procedure.

Pharmaceutically acceptable salts include, for example, salts with acids forming physiologically acceptable anions, such as salts with mineral acids, for example, hydrogen halides (such as hydrogen chloride and hydrogen bromide), sulfonic and phosphonic acids, and with organic acids such as acetic acid, oxalic acid, tartaric acid, p-toluenesulfonic acid, methanesulfonic acid, trifluoroacetic acid and the like.

The coupling reaction is suitably carried out under conditions under which the amino groups in the compounds of formula (II) and (III) remain protonated, for example, at slightly acid pH values, for example independently selected from below pH 6, or below pH 5.. Whilst we don't wish to be limited by theoretical considerations it is believed that below pH 9, for example below pH 8 or below pH 7 the amino groups will be substantially in the protonated form.

Anions X and X' may be the same or different, but are preferably the same. In particular, these are anions which form pharmaceutically acceptable salts as described above, and preferred examples are halides such as chloride.

Preferably R^3 is hydrogen.

Where R^3 is a protecting group for an amino group of an acetamide moiety, it may be any protecting group known in the art to be useful for such a group. Examples may be found for instance in J Jones, The Chemical Synthesis of Peptides, Clarendon Press, Oxford, 1994; T Greeve, P Wuts, Protective Groups in Organic Synthesis, J Wyley & Sons, 3rd Edition, 1999; and Bodanszky and Bodanszky, The Practice of Peptide Synthesis, Springer, 2nd Edition, 1994; the disclosures of which are hereby incorporated by reference. A particular value for R^3 when it is a protecting group is benzyl.

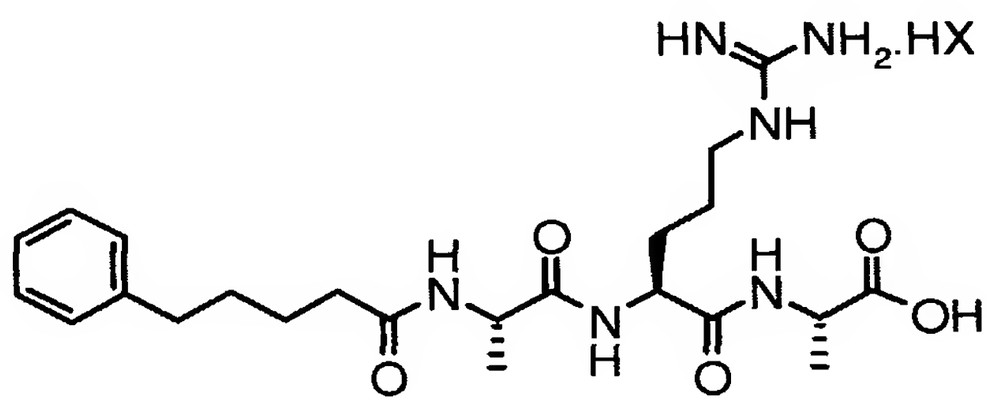
The coupling reaction is carried out using any standard procedure known in the art for coupling acids with amines to form amides. Such procedures are, for example, described in Bodansky and Bodansky (*supra*), the disclosures of which are incorporated herein by reference. In particular, for example, the coupling is suitably carried out in an organic solvent such as N,N-dimethylformamide (DMF), dichloromethane (DCM), N-methylpyrrolidinone (NMP) or tetrahydrofuran (THF) in the presence of a coupling reagent. Typical coupling reagents include, for example, dicyclohexylcarbodiimide (DCCI), diisopropylcarbodiimide (DIC) or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI) in

the presence of 1-hydroxybenzotriazole (HOBt), or 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, in the presence of a tertiary amine base such as N-methylmorpholine (NMM) or diisopropylethylamine (DIPEA). Preferably EDCI and HOBt in the presence of DCM and DMF are used. When EDCI is used as the coupling agent it is preferably in the form of the hydrochloride addition salt. When the coupling is performed in the presence of HOBt, the HOBt is preferably used in the form of its monohydrate.

Typically the coupling is initially carried out at low temperature, for example in the range of -5°C to +5°C, and the reaction mixture can be allowed to attain ambient temperature.

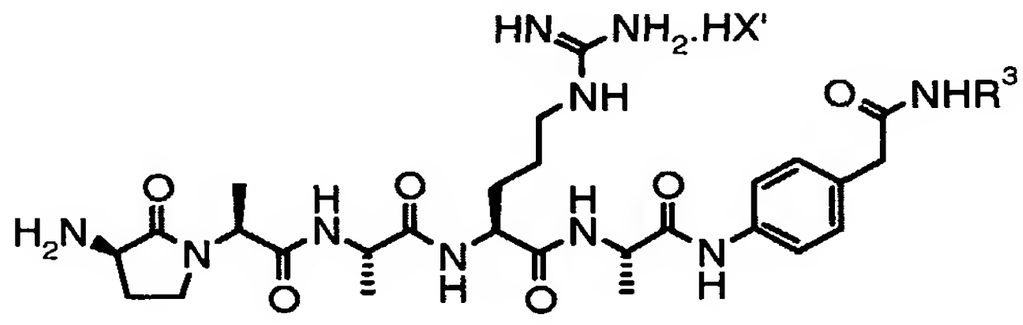
In a preferred embodiment the coupling is performed in DMF or NMP at a temperature of less than 0°C, for example in the range of from 0 to –5°C. It is especially preferred that the coupling is performed in DMF at a temperature in the range of from 0 to –5°C.

In one embodiment, the process of the invention comprises the preparation of a salt of a compound of formula (I) by coupling a carboxylic acid of the formula (IV) or a salt thereof,



(IV)

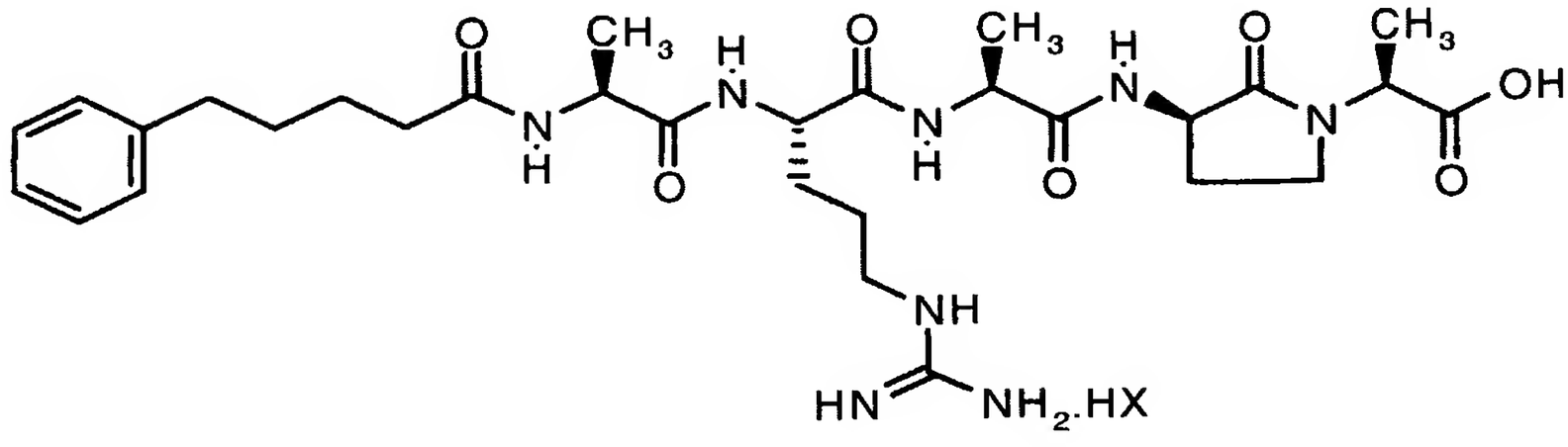
wherein X is as defined above, with an amine of the formula (V)



(V)

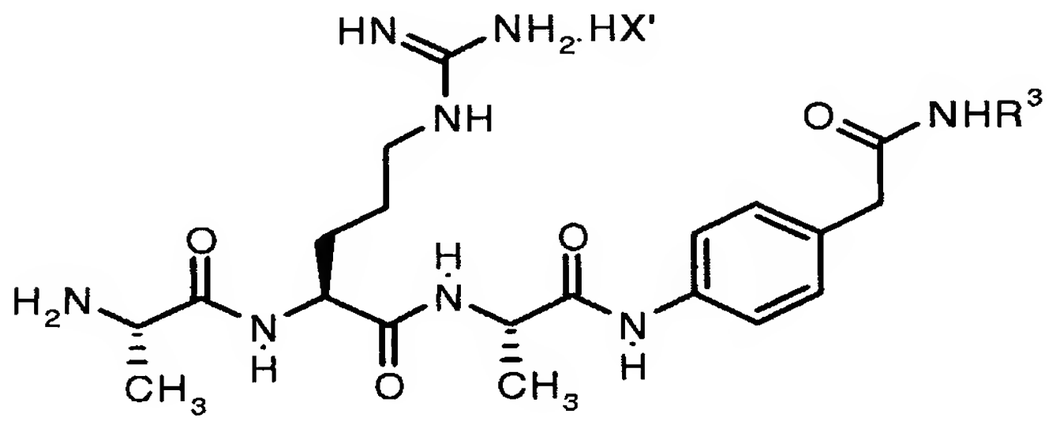
wherein X' and R^3 are as defined above.

In an alternative embodiment, the process comprises coupling a carboxylic acid of the formula (VI) or a salt thereof,



(VI)

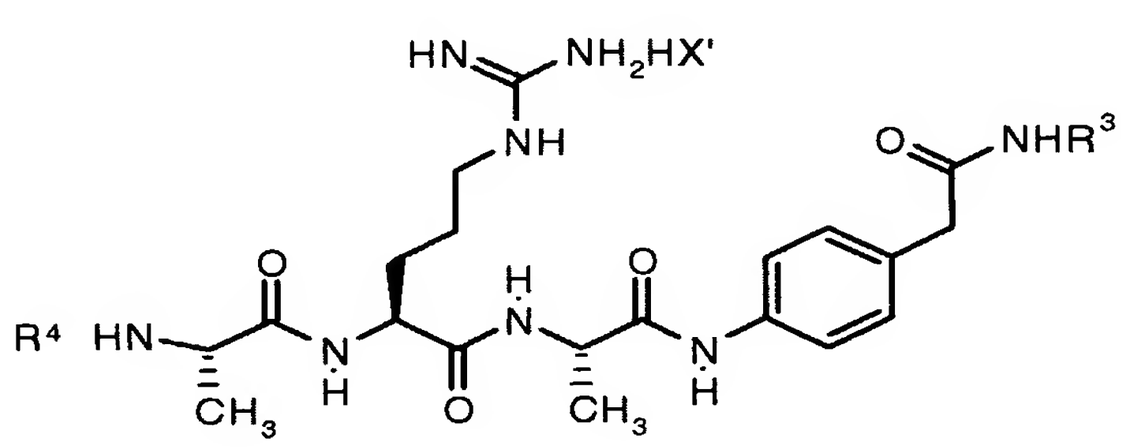
wherein X is as defined above with an amine of the formula (VII) or a salt thereof



(VII)

wherein X' and R^3 are as defined above. Preferably both X and X' are halide such as chloride and R^3 is hydrogen.

Preferably the compound of formula (VII) is generated from an amine protected form thereof, for example from a compound of the formula (VIII)



(VIII)

wherein R^3 is as defined above (and is preferably hydrogen), X^I is as defined above (and is preferably chloride), and R^4 is an amino protecting group. It is important that R^4 is chosen such that it can be selectively removed in the presence of X^I and R^3 if the latter is other than

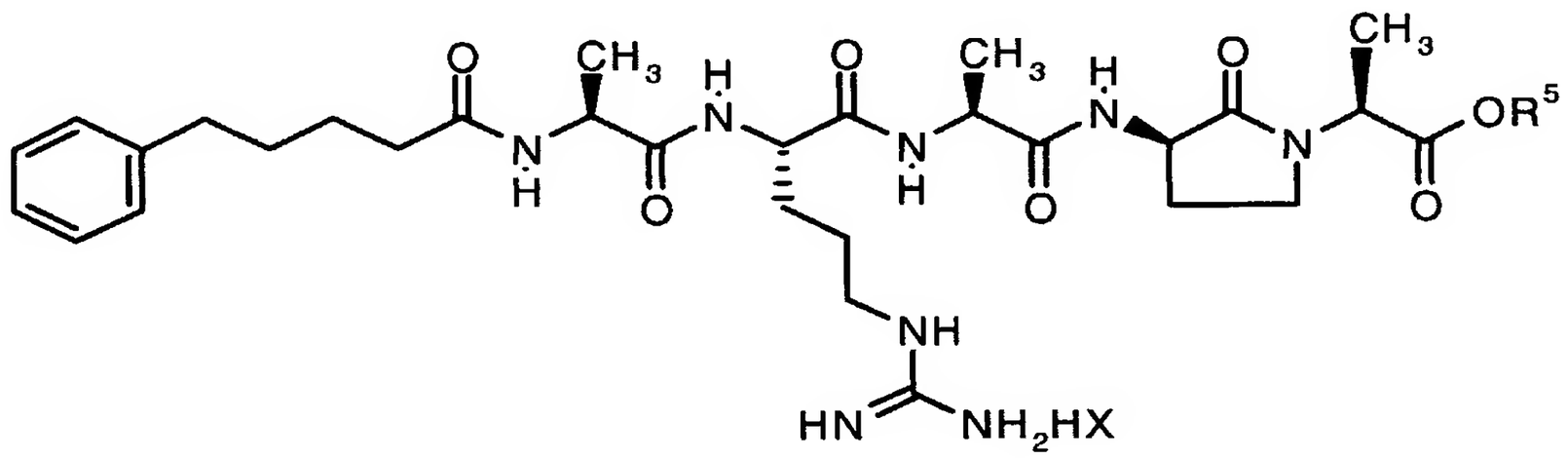
hydrogen. A particular example of R^4 is the benzyloxycarbonyl group. This protecting group can then be removed by hydrogenation.

Catalytic hydrogenation is especially preferred. A suitable catalyst for catalytic hydrogenation includes, for example, palladium on charcoal, platinum oxide, palladium black and palladium salts such as Pd(II) acetate. The catalytic hydrogenation is conveniently carried out in the presence of a solvent or mixture of solvents. Suitable solvents include, for example, aqueous alcohols and especially aqueous ethanol. The use of aqueous ethanol (preferably in the ratio of ethanol to water of 20:1 to 3:1 v/v, more preferably about 6:1 v/v) is particularly preferred. A particularly preferred catalyst for catalytic hydrogenation includes 3-20% palladium on charcoal, for example 5-10% palladium on charcoal, or palladium on zeolite or silica. The catalysts are preferably used in an amount such that there is 0.3 to 1.2% w/w palladium per compound of formula (VIII). The hydrogenation is preferably carried out at a hydrogen pressure of 0-100 bar gauge, and preferably at 0-10 bar gauge and especially from 1 to 5 bar gauge. Conveniently the catalytic hydrogenation is carried out at a temperature in the range of, for example, 10-70°C, preferably 20-50°C.

Other suitable values for X', R^3 and R^4 which allow selective removal of R^4 in the presence of X' and R^3 if the latter is other than hydrogen are well known in the art.

Preferably in this process, R^3 is hydrogen and X is chloride.

Preferably a compound of formula (VI) or a salt thereof as defined above is prepared by hydrolysis of an ester of formula (IX)

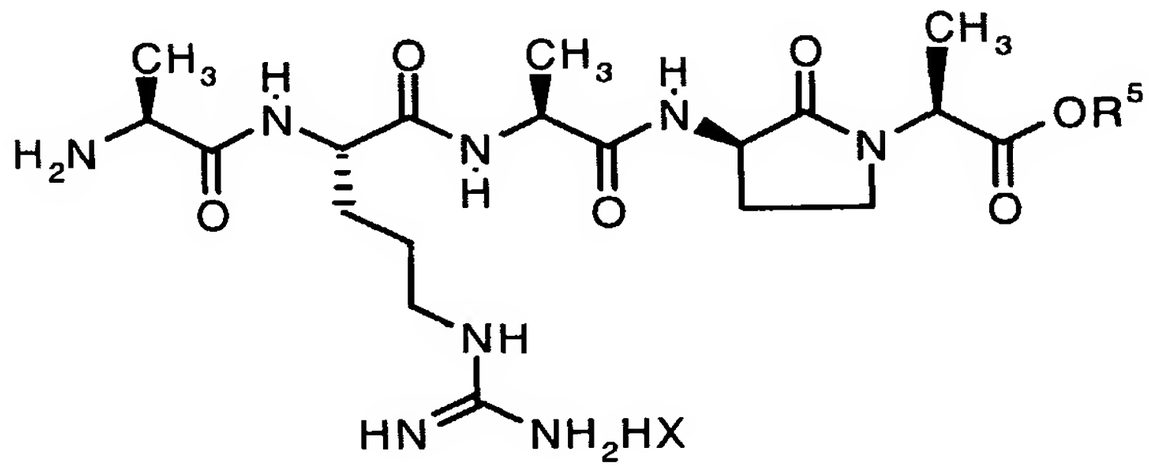


(IX)

wherein R^5 is alkyl, for example (1-6C)alkyl, or aralkyl (for example phenyl(1-6C)alkyl such as benzyl) and X is as defined above (preferably chloride). Typically the hydrolysis is carried out under aqueous base conditions, for example using an aqueous solution of an alkali metal hydroxide (such as sodium hydroxide or lithium hydroxide) and a suitable organic solvent

(such as acetonitrile). The hydrolysis is conveniently carried out at ambient temperature. The reaction mixture is subsequently acidified, for example using hydrochloric acid, to give the free acid.

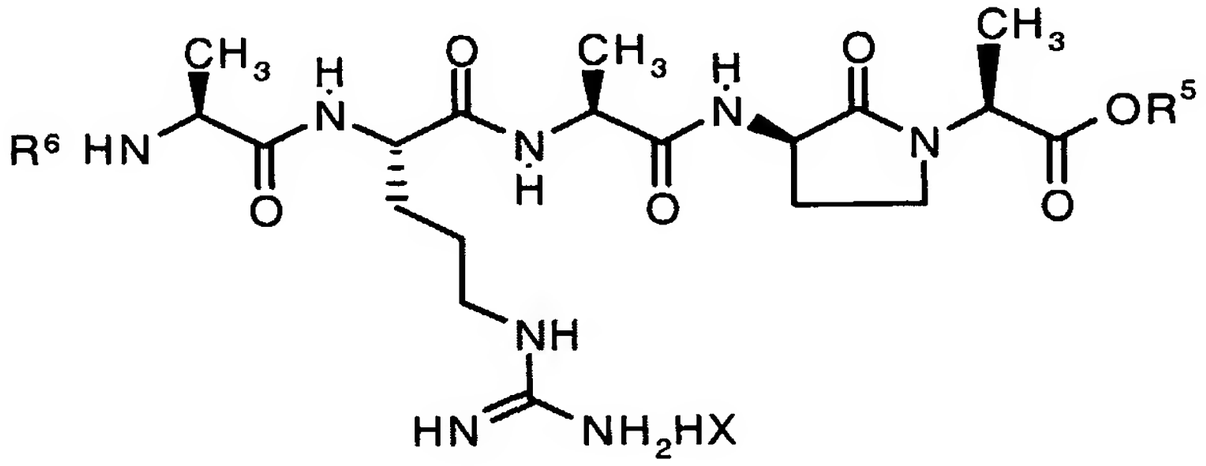
A compound of the formula (IX) may be obtained by coupling an amine of formula (X) or a salt thereof



(X)

wherein R^5 and X are as defined above, with 5-phenylvaleric acid. Suitable coupling conditions are analogous to those described above for the coupling of compounds of formula (II) and (III). In particular the reaction is effected in the presence of coupling agents HOBt and EDCI, in a solvent comprising DMF and/or DCM.

Compounds of formula (X) are suitably prepared by deprotection of a compound of formula (XI)

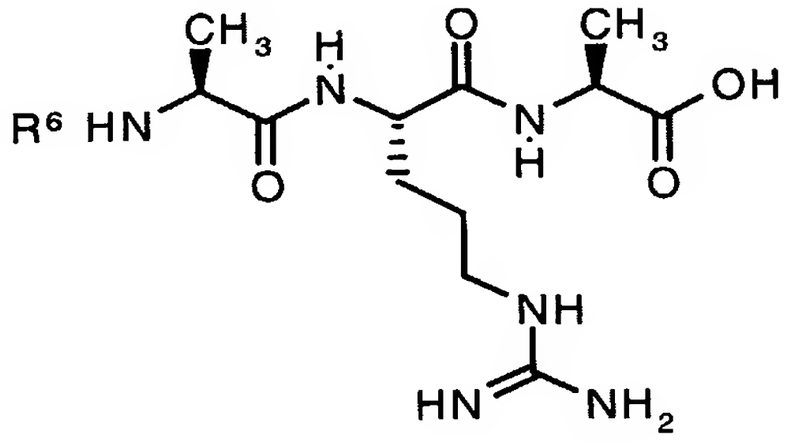


(XI)

where R^5 and X are as defined above, and R^6 is an amine protecting group, as defined above in relation to R^4. In particular, R^6 is a benzyloxycarbonyl group.

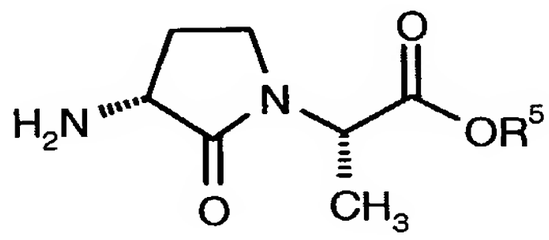
Deprotection of the compound of formula (XI) is suitably effected by catalytic hydrogenation using methods analogous to those described above for removal of group R^4 from the compound of formula (VIII).

Compounds of formula (XI) are suitably prepared by coupling together a carboxylic acid of formula (XII) or a salt thereof



(XII)

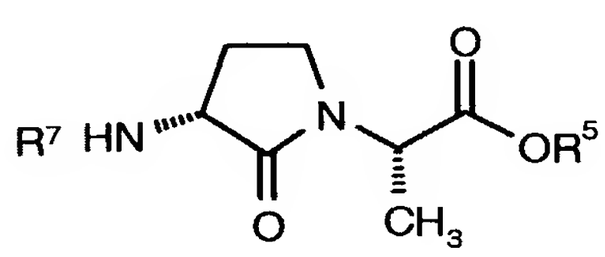
where R^6 is as defined above, with a compound of formula (XIII) or a salt thereof



(XIII)

wherein R^5 is as defined above, and in particular is methyl. Coupling may be effected using conditions analogous to those described above for the coupling of compounds of formula (II) and (III). Particular solvents in this case are DCM and/or DMF, and coupling agents are EDCI and HOBt in the presence of DIPEA. Preferably the temperature during this coupling reaction is 0°C or less, more preferably from 0 to –10°C and especially from 0 to –5°C.

Compounds of formula (XIII) are suitably obtained by removing the group R^7 from a compound of formula (XIV)



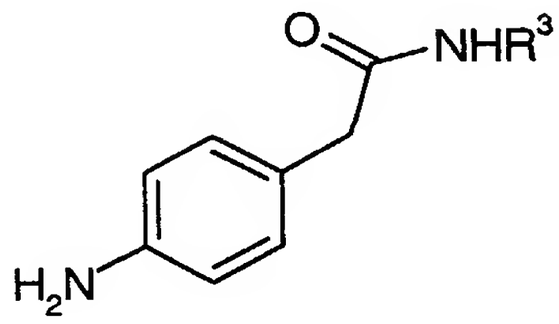
(XIV)

where R^5 is as defined above and R^7 is an amino protecting group. Suitable amino protecting groups in this case include those which can be readily removed in the presence of R^5. Preferably the amino protecting group R^7 is one which can be readily removed under acidic conditions, such as a tert-butyloxycarbonyl (Boc) group. This protecting group can be removed using, for example, hydrogen chloride or an organic acid such as trifluoroacetic

acid, formic acid, or an aryl sulphonic acid. Suitable aryl sulphonic acids include, for example toluene sulphonic acid or, more preferably, benzene sulphonic acid. It is especially preferred that trifluoroacetic acid or formic acid is used to remove R^7 when it is Boc. The product in this case is a salt of formula (XIII), for example, the trifluoroacetate salt.

The compound of formula (XIV) may be prepared using known methods, for example as described in Example 1 of WO 97/31023 or by the process described in WO 99/55669. Alternatively, we have found that the compound of formula (XIV) may be prepared by an analogous process to those of the cited references but using an alternative methylating agent, for example dimethylsulfate.

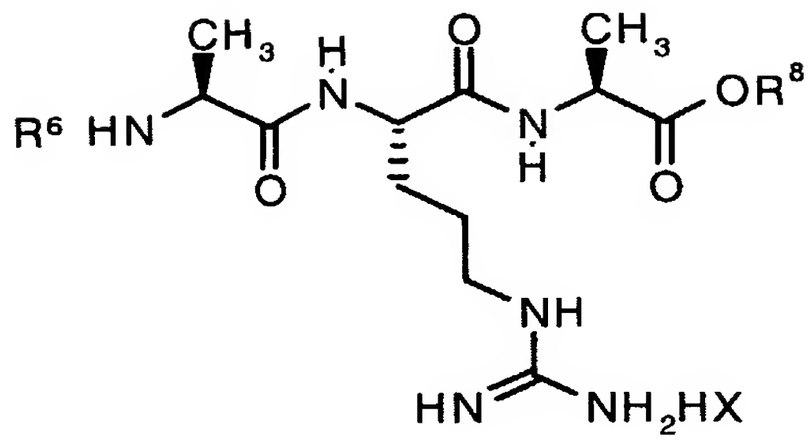
A compound of the formula (XII) may also be used in the preparation of a compound of formula (VIII) above. In this case, the compound of formula (XII), is coupled with a compound of formula (XV)



(XV)

wherein R^3 is as defined above and in particular is hydrogen or benzyl, and preferably hydrogen, and the product obtained in the form of the desired salt. The coupling may be carried out using methods analogous to those described above in relation to the coupling of compounds of formula (II) and (III). In particular, the coupling is effected using HOBt and EDCI as coupling agents, in a solvent such as DMF and DCM. Again, low temperatures for example of from 0-5°C are employed. The product may be obtained as the desired salt by ensuring that the requisite ions are present in the reaction mixture, for example, the EDCI may be added in the form of the hydrochloride salt to produce a compound of formula (VIII) where X is chloride.

A compound of formula (XII) is preferably obtained by hydrolysis of an ester of formula (XVI)

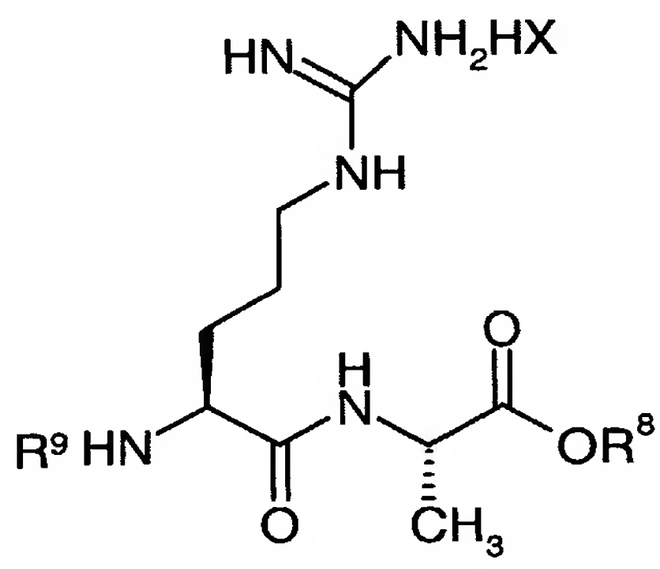


(XVI)

wherein R^6 and X are as defined above and R^8 is alkyl, for example (1-6C)alkyl, or aralkyl (for example phenyl(1-6C)alkyl such as benzyl). This reaction is suitably effected under conditions analogous to those described for the hydrolysis of the ester of formula (IX).

Thus compounds of formula (XII) are common intermediates for use in the production of both compounds of formula (VIII) and (XI). This provides a significant degree of economy in the process.

Compounds of formula (XVI) are suitably prepared by selective removal of a protecting group R^9 from a compound of formula (XVII) and coupling the product with a R^6 protected (S)-alanine:



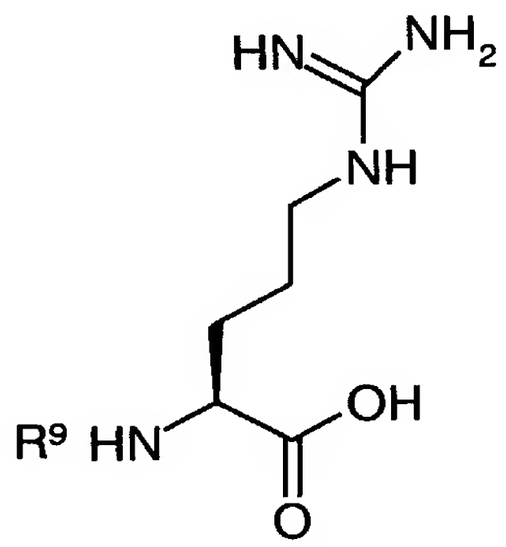
(XVII)

wherein R^9 is an amino protecting group which can be selectively removed in the presence of X and R^8. Suitable groups represented by R^9 are as hereinbefore defined for R^6, preferably benzyloxycarbonyl. Preferably in formula (XVII), X is chloride, R^8 is methyl and R^9 is benzyloxycarbonyl. As will be understood, R^6 in the R^6 protected (S)-alanine is a protecting

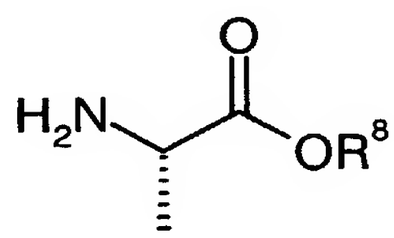
group for the amine in the (S)-alanine. Preferably R^9 and R^6 are the same, more preferably R^9 and R^6 are both benzyloxycarbonyl. R^8 is preferably (1-4C)alkyl, more preferably methyl.

The conditions for the removal of R^9 are analogous to those described above for the removal of R^6 from the compound of formula (XI). Following removal of R^9 from the compound of formula (XVII), the conditions for the coupling with the R^6 protected (S)-alanine are analogous to those described above for the coupling of the compounds of formula (II) and (III). When R^9 is benzyloxycarbonyl, it is preferably removed using catalytic hydrogenation.

A compound of formula (XVII) may be obtained from the coupling of a compound of the formula (XVIII) or a salt thereof, and a compound of the formula (XIX) or a salt thereof:



(XVIII)



(XIX)

wherein R^8 and R^9 are as hereinbefore defined, in the presence of a suitable acid of formula HX, so as to give a protonated product. As before, X is preferably chloride, R^9 is preferably benzyloxycarbonyl and R^8 is preferably methyl. The acid HX may be added to the reaction mixture, or alternatively, appropriate acid addition salts of compounds of formula (XIX) or (XVIII) may be employed in the process to achieve the same result. Suitable conditions for the coupling of the compounds of formula (XVIII) and (XIX) are analogous to those used for the coupling of the compounds of formulae (II) and (III) described above.

It is preferred that the compound of formula (XVII) is isolated in crystalline form prior to subsequent reaction because this minimises the formation of undesirable impurities. However, if desired the coupling of the compounds of formula (XVIII) and (XIX) followed by deprotection and coupling with the R^6 protected (S)-alanine may be telescoped together.

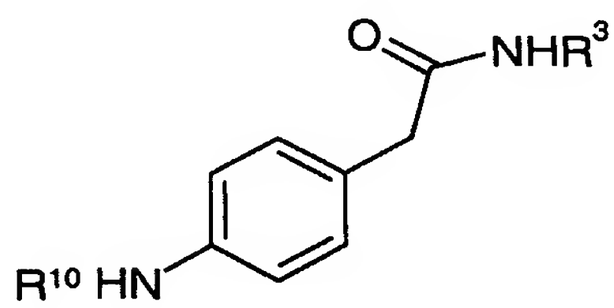
4-Aminophenylacetamide (formula XV, R^3 is H) may be obtained, for example, as described in the examples hereinafter. A preferred process for the preparation of 4-aminophenylacetamide comprises the steps:

(i) esterification of 4-aminophenylacetic acid with a suitable alcohol in the presence of sulphuric acid to give a 4-aminophenylacetate ester hydrogensulphate salt; and

(ii) reacting the product of step (i) with ammonia.

The alcohol used in step (i) is preferably a (1-4C)alkanol for example ethanol or, more preferably, methanol. A suitable reaction temperature for step (i) is less than 30°C, more preferably less than 25°C. Step (ii) of this process is preferably carried out in an aqueous medium, more preferably in water containing dissolved sodium chloride. Preferably aqueous ammonia is added to an aqueous solution of the product of step (i). Preferably the product of step (i) is isolated in a crystalline form prior to step (ii) of the process. The product of step (i) may be crystallised from a suitable solvent, for example from methyl tert-butyl ether. We have found that this preferred process provides 4-aminophenylacetamide in high yield and in pure form.

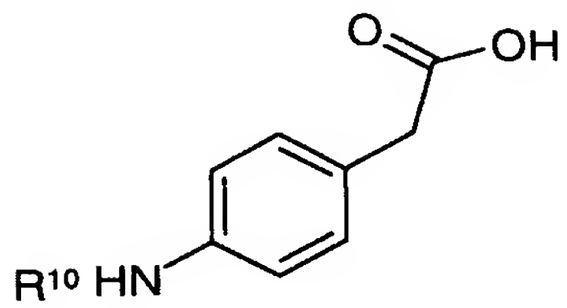
A compound of the formula (XV) in which R^3 is a protecting group, such as benzyl, may be obtained for example by removal of the amino protecting group R^{10} from the compound of the formula XVa, wherein R^{10} is an amine protecting group as hereinbefore defined for R^7 (for example Boc):



(XVa)

wherein R^3 is as hereinbefore defined. The protecting group R^{10} may be removed using analogous conditions to those described above for the removal of R^7.

The compound of the formula XVa may be prepared for example by coupling the compound of the formula XVb



(XVb)

wherein R^{10} is as defined above, with a compound of the formula R^3NH_2 wherein R^3 is a protecting group as hereinbefore defined.

For example, when R^3 in the compound of formula (XV) is benzyl this compound may be prepared by coupling 4-(butyloxycarbonylamino)phenylacetic acid with benzylamine, followed by removal of the Boc group under acidic conditions. Analogous coupling conditions to those described above for the coupling of compounds of formula (II) and (III) may be used in these cases. A suitable solvent for this coupling reaction includes, for example tetrahydrofuran.

Compounds of formula (IV) and (V) above may be prepared using processes analogous to those described herein, as would be apparent to the skilled person.

Certain compounds listed above are novel and these, together with processes for their preparation form a further aspect of the invention. Thus the invention further provides a compound of formula (IV), (V), (VI), (VII), (VIII), (IX), (X), (XI), (XVI), and (XVII) are novel compounds and these, in particular where the groups X or X' are chloride, together with the methods of preparation described above, form further aspects of the invention.

The invention will now be illustrated by the following non-limiting examples in which, unless otherwise stated:-

(i) concentrations and evaporations were carried out by rotary evaporation in vacuo;

(ii) operations were carried out at room temperature, that is in the range 18-26°C;

(iii) yields, where given, are intended for the assistance of the reader only and are not necessarily the maximum attainable by diligent process development;

(iv) ^{1}H NMR spectra were determined using tetramethylsilane (TMS) as an internal standard, and are expressed as chemical shifts (delta values) in parts per million relative to TMS using conventional abbreviations for designation of major peaks: s, singlet; d, doublet; m, multiplet; t, triplet; br, broad.

Preparation 1

Preparation of 4-Aminophenylacetamide:

The 4-Aminophenylacetamide used in this example was obtained as follows:

(i) Methanol (200 ml) was charged to 4-aminophenylacetic acid (25.0 g). Sulfuric acid (18.0 ml) was added maintaining the temperature <20°C. The mixture was then refluxed for one hour and concentrated by distillation at atmospheric pressure until a volume of 135 ml. The mixture was then cooled to 50°C and methyl tert-butyl ether (275 ml) added maintaining the temperature above 45°C. The mixture was then gradually cooled to 0-5°C and held at this temperature for 1 hour. The resultant crystalline product was isolated by filtration and washed with cold methanol : methyl tert-butyl ether (20 ml : 55 ml) and cold methyl tert-butyl ether (75 ml) then dried under vacuum at 45°C to give methyl 4-aminophenylacetate hydrogensulfate (40.1 g);

^{1}H NMR (d_6-DMSO): 3.61 (s, 3H), 3.71 (s, 2H), 7.25 (m, 2H), 7.35 (m, 2H).

(ii) Methyl 4-aminophenylacetate hydrogensulfate (20 g) was added to 20% w/w aqueous sodium chloride (37.5 g). Aqueous ammonia (density 0.88 g/ml 50 ml) containing dissolved sodium chloride (7.5 g) was added maintaining the temperature 15 - 25°C. The mixture was then stirred for 16 hours at 22°C. The mixture was cooled to 0-5°C and held at this temperature for one hour. The resultant crystalline product was isolated by filtration, washed with water (2 x 20 ml), and dried under vacuum at 45°C to give 4-aminophenylacetamide (7.2 g);

^{1}H NMR (d_6-DMSO): 3.16 (2H), 4.85 (2H), 6.49 (2H), 6.90 (2H).

Example 1

The preparation described in this Example is summarised in the attached scheme.

Step (i)

Preparation of carbobenzyloxy-(S)-arginyl-(S)-alanine methyl ester hydrochloride (Compound of formula (XVII) where R^9 is benzyloxycarbonyl, X is chloride and R^8 is methyl).

Benzyloxycarbonyl-(S)-arginine (10.0 g), (S)-alanine methyl ester hydrochloride (4.53 g)

and 1-hydroxybenzotriazole hydrate (0.5 g) were slurried in a mixture of acetonitrile (54 l) and water (6 ml) and cooled to 0-5°C. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (6.52 g) was added in one portion and the contents stirred for 3 hours to complete the reaction. A solution of citric acid (10.0 g) and salt (21.2 g) in water (100 ml) was added, and the organic phase separated. The aqueous phase was re-extracted twice with acetonitrile (60 ml) and the combined extracts washed with saturated brine solution (50 ml). The organic phase was doubled in volume by the addition of acetonitrile (155 ml) and distilled, collecting 170 ml of distillates. The remaining solution was cooled to 0-5°C and seeded. The crystalline solid was collected by filtration washed twice with cold acetonitrile (20 ml) and MTBE (100 ml) and dried at 40 to 45°C under vacuum to constant weight to give carbobenzyloxy-(S)-arginyl-(S)-alanine methyl ester hydrochloride (10.6 g).

1H NMR (d_6-DMSO): 7.30 m (5H), 5.20 s (2H), 4.40 q (1H), 4.19 t (1H), 3.69 s (3H), 3.20 t (2H), 1.82 m (1H), 1.68 m (3H), 1.40 d(3H)

Step (ii)

Preparation of a Zwitterion of a Compound of formula (XVI) where R^6 is benzyloxycarbonyl, and R^8 is methyl

The product of step (i) (1.2 g) and 5% palladium on carbon (120 mg, 50% water wet) was added to ethanol (12 ml). The mixture was stirred under a positive pressure of hydrogen in the presence of concentrated hydrochloric acid (0.24 ml). The mixture was filtered through a celite bed and the filtrates concentrated to give a white solid. The solid was added to dichloromethane (10 ml). To the resulting suspension was added benzyloxycarbonyl-(S)-alanine (0.6 g) and diisopropylethylamine (0.5 ml). The reaction mixture was cooled to 5°C, and 1-hydroxybenzotriazole monohydrate (0.6 g) was then added, followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.6 g). The mixture was stirred at 5°C for 15 minutes then warmed to room temperature for 4 hours. The solution was washed with sodium chloride solution (10 ml). The aqueous phase was extracted with isobutanol (10 ml). The isobutanol solution was washed with sodium chloride solution (10 ml), concentrated by evaporation, and filtered. The filter cake was washed with isobutanol (5 ml), and the combined filtrate concentrated by evaporation to give an oil. MTBE (25 ml)

was added to the oil to precipitate a white solid. The product was collected by filtration, washed with MTBE (5 ml) and dried under vacuum.

^{1}H NMR (CD_3OD): 1.4 (dd, 6H), 1.8 – 2.0 (m, 4H), 3.3 (m, 2H), 3.8 (s, 3H), 4.2 (q, 1H), 4.4 (q, 2H), 5.1 (s, 2H), 7.4 (m, 5H)

Step (iii)

Preparation of Compound of Formula (XII) where R^6 is benzyloxycarbonyl and X is chloride

A stirred solution of the product of step (ii) (44 g) in acetonitrile (363.4 ml) at 40°C-45°C was cooled to room temperature and a 5M aqueous sodium hydroxide solution (19.7 ml) was added. The mixture was stirred overnight (18 hours) at room temperature, filtered, washed twice with aqueous acetonitrile (8 ml water + 32 ml acetonitrile) and then acetonitrile (40 ml). The filtered solid was dried at 40°C under vacuum to give the title compound in 86% wt yield.

^{1}H NMR (269.60 MHz, CD_3OD): δ1.3 (d, 3H), δ1.44 (d, 3H), δ 1.6-1.95 (m, 4H), δ 3.15 (t, 2H), δ 3.47 (s, 2H), δ 3.58 (q, 1H), δ 4.45 (m, 2H), δ 7.24 (d, 2H), δ 7.50 (d, 2H).

Step (iv)

Preparation of Compound of Formula (VIII) where R^4 is benzyloxycarbonyl, R^3 is hydrogen and X^I is chloride

A suspension of the product of step (iii) zwitterion (1.5 g) in water (22.5 ml) at room temperature was treated with trifluoroacetic acid (265 μL) to pH 2. The solution was concentrated to an oil, which was dissolved in dichloromethane (25 ml) and then concentrated in vacuum to a semi solid. The material was dissolved in a mixture of dichloromethane (18 ml) and dimethylformamide (6.0 ml) at room temperature, then treated with 1-hydroxybenzotriazole monohydrate (0.168 g) and 4-aminophenylacetamide (see Preparation 1 above)(0.45 g). The solution was chilled to 0-5°C and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.58 g) added at 0-5°C. The stirred suspension was allowed to warm to room temperature overnight, then treated with water (18 ml). The separated aqueous layer was washed with ethyl acetate (3 x 12 ml), before addition of salt (3.0 g) and water (21 ml), and extraction of the product into *iso*-butanol (3 x 21 ml). After organic solvent removal in vacuum and re-evaporation from toluene (20 ml), the product was solidified by trituration with acetone (100 ml). After stirring overnight, the

product was de-liquored by filtration and re-slurried with acetone (50 ml). The product was filtered, washed with MTBE (25 ml) and dried under vacuum at 40 °C to give the tetrapeptide (i.e. the title compound) (0.92 g).

^{1}H NMR (CD_3OD): 1.45 (d, 3H), 1.52 (d, 3H), 1.75 (m, 2H), 1.85 (m, 1H), 2.00 (m, 1H), 3.25 (m, 2H), 3.58 (m, 2H), 4.23 (q, 1H), 4.52 (m, 2H), 5.20 (m, 2H), 7.32 (d, 2H), 7.40 (d, 5H), 7.61(d, 2H).

Step (v)

Preparation of Compound of Formula (XI) where R^6 is benzyloxycarbonyl, X is chloride and R^5 is methyl

Methyl-(S)-2-[(R)-3-(N-[tert-butyloxycarbonyl]amino-2-oxopyrrolidin-1-yl] propionate (Compound of formula XIV where R^7 is tert-butyloxycarbonyl, R^5 is methyl)(0.6185 g) was dissolved in dichloromethane (60 ml) and excess dry hydrogen chloride gas was passed through the solution for 15 minutes at room temperature. The solution was stirred at room temperature until the deprotection was complete by HPLC analysis. The solvent was removed by evaporation in vacuum. The resulting solid methyl ((S)-2-[(R)-3-(amino-2-oxopyrrolidin-1-yl] propionate) was dissolved in dichloromethane (16 ml).

A suspension of the product of step (iii) zwitterion (1.2 g) in water (18 ml) at room temperature was treated with trifluoroacetic acid (200 µL) to pH 2. The solution was concentrated in vacuum to an oil, which was dissolved in dichloromethane (20 ml) and then concentrated in vacuum to a semi-solid. This was dissolved in dimethylformamide (4.0 ml) and mixed with the dichloromethane solution of the methyl ((S)-2-[(R)-3-(amino-2-oxopyrrolidin-1-yl] propionate) (prepared above). The solution at room temperature was treated with 1-hydroxybenzotriazole monohydrate (0.066 g) and di-*iso*propylethylamine (0.4 ml). The suspension was chilled to 0-5 °C and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.455 g) was added, allowing the reaction mixture to warm slowly to room temperature overnight.

After evaporation of solvents under high vacuum, the product was partitioned between water (30 ml) and ethyl acetate (10 ml). The separated aqueous phase was washed with further ethyl acetate (2 x 10 ml) and the product extracted from the aqueous phase with *iso*-butanol (3 x 12 ml). After organic solvent removal by evaporation under high vacuum,

the oil was solidified by successive treatment with acetone (100 ml) and MTBE (100 ml) to give the crude pentapeptide of formula (XI) where R^6 is benzyloxycarbonyl, X is chloride and R^5 is methyl) (1.39 g).

^{1}H NMR (CD_3OD): 1.43 (d, 3H), 1.48 (d, 3H), 1.53 (d, 3H), 1.75 (m, 2H), 1.85 (m, 1H), 2.00 (m, 2H), 2.55 (m,1H), 3.28 (m, 2H), 3.55 (m, 2H), 3.81 (s, 3H), 4.23 (q, 1H), 4.45 (m, 2H), 4.58 (t, 1H), 4.82 (m, 1H), 5.20 (m, 2H), 7.45 (m, 5H).

Step (vi)

Preparation of Compound of formula (IX) where X is chloride and R^5 is methyl

The product of step (v) as the hydrochloride salt (0.25 g) and 10% palladium on carbon (25 mg) were added to a mixture of water (0.5 ml), and ethanol (5 ml), and the mixture was agitated under a positive pressure of hydrogen for 20 hours. The mixture was filtered through a celite bed. The vessel and cake were washed with ethanol (5 ml), and the combined fitrates concentrated by evaporation to give an oil. The oil was dissolved in dichloromethane (5 ml), and DMF (3 ml). To this solution was added 5-phenylvaleric acid (70 mg), and 1-hydroxybenzotriazole monohydrate (6 mg). The mixture was cooled to 5°C and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (80.5 mg) was added. The mixture was warmed to room temperature and agitated for 24 hours. The solution was concentrated by evaporation to an oil, which was dissolved in isobutanol (2 ml) and washed with dilute brine (2 ml). The solution was concentrated and a white solid obtained by trituration with a mixture of MTBE (5 ml) and ethyl acetate (5 ml). The solid was collected by vacuum filtration to give the desired product as the hydrochloride salt (110 mg).

^{1}H NMR (CD_3OD): 1.45 (t, 6H), 1.6 (d, 3H), 1.8 – 2.1 (m, 8H), 2.43 (t, 2H), 2.60 (m, 2H), 2.77 (t, 2H), 3.32 (m, 2H), 3.60 (m, 2H), 3.86 (s, 3H), 4.42 (m,1H), 4.5 (m, 2H), 4.62 (m, 1H), 4.9 (m, 1H), 7.35 (m, 5H)

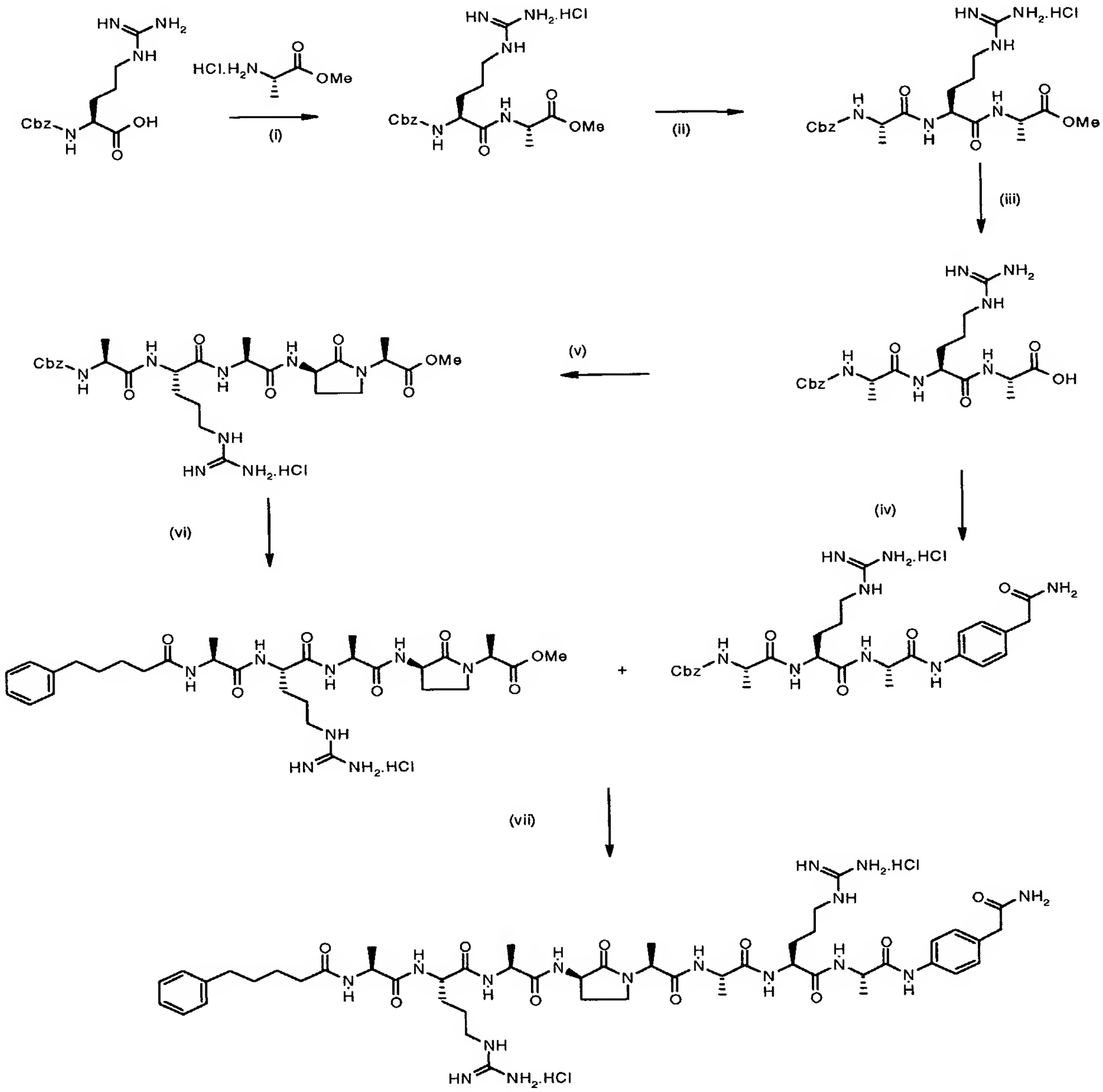
Step (vii)

Preparation of Dihydrochloride salt of Formula (I)

The product of step (iv) (0.27 g) and 10% palladium on carbon (27 mg) was added to a mixture of ethanol (3 ml) and water (0.5 ml), and stirred under a positive pressure of hydrogen at room temperature for 4 hours. The reaction mixture was filtered through a celite pad. The vessel and pad were washed with a mixture of ethanol (3 ml) and water (0.5

ml). The combined filtrates were concentrated by evaporation to a yellow oil. The oil (compound of formula (VII) where R^3 is hydrogen and X' is chloride) was dissolved in a mixture of DMF (4 ml) and dichloromethane (2 ml).

The product of step (vi) (300 mg) was dissolved in a mixture of acetonitrile (3 ml) and water (1.5 ml), 1M sodium hydroxide (0.44 ml) was added and the mixture stirred at room temperature for 3 hours. 1M Sodium hydroxide (0.16 ml) was added and the mixture stirred at at room temperature for 1 hour. 1M Hydrochloric acid (0.6 ml) and saturated brine solution (6 ml) were added and then the mixture was extracted with isobutanol (12 ml and 6 ml). The combined extracts were concentrated by evaporation to give an oil. The oil was dissolved in DMF (2 ml) and added to the above solution of the resultant compound of formula (VII) prepared above. This mixture was chilled to 5°C and 1-hydroxybenzotriazole monohydrate (12 mg) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (93 mg) was added. The mixture was stirred at 5°C for 4 hours before concentrating by evaporation to a brown oil. The oil was dissolved in isobutanol (12 ml), and washed with a mixture of brine solution (2.5 ml) and water (2.5 ml). The organic phase was retained and the aqueous phase was extracted with isobutanol (5 ml). The combined organic solutions were washed with water (2 ml), then concentrated by evaporation to give a gum. The gum was partially dissolved in warm ethanol (10 ml), then added to ethyl acetate to precipitate a white solid. The solid was collected by fitration, washed with ethyl acetate (10 ml) and dried under vacuum to give the compound of formula (I) as the dihydrochloride salt.



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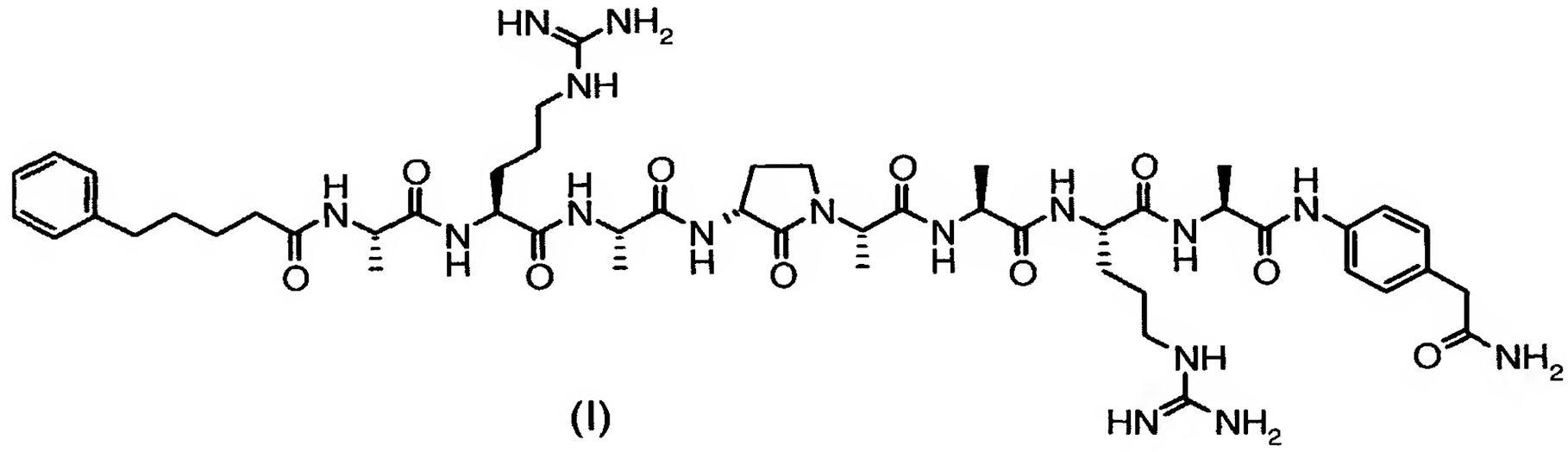
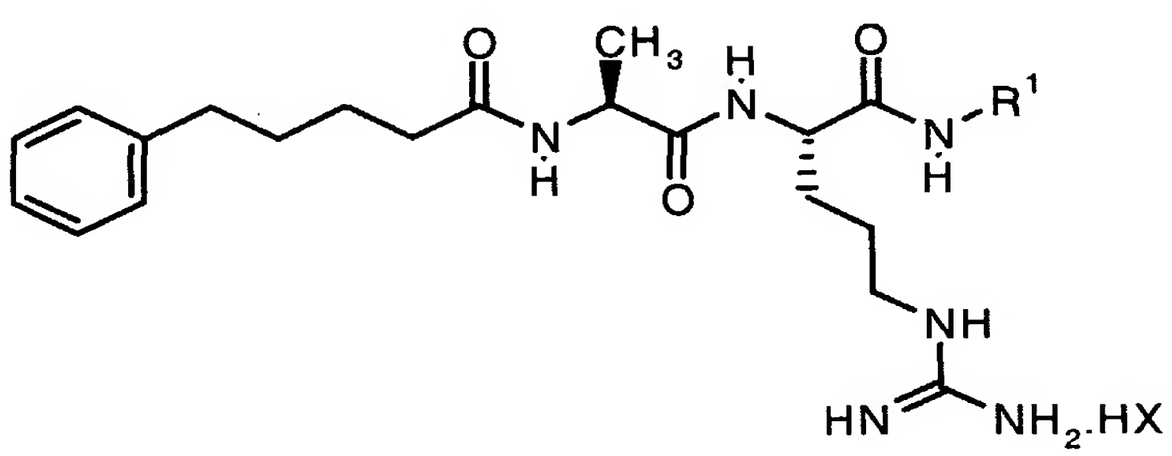
CIAIMS

1. A process for the manufacture of a salt of the compound of formula (I)



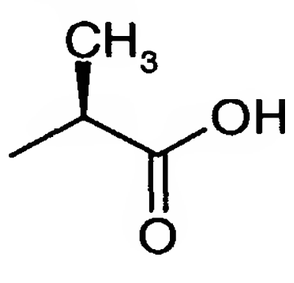
(I)

which process comprises coupling together a carboxylic acid of formula (II) or a salt thereof:



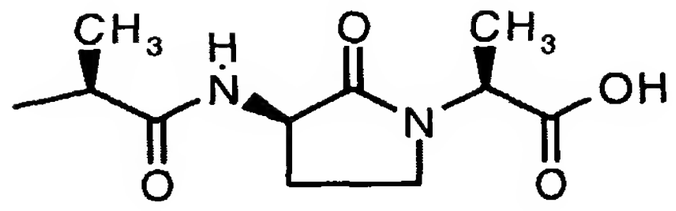
(II)

where X is a anion, and R^1 is either a group of sub-formula (i)



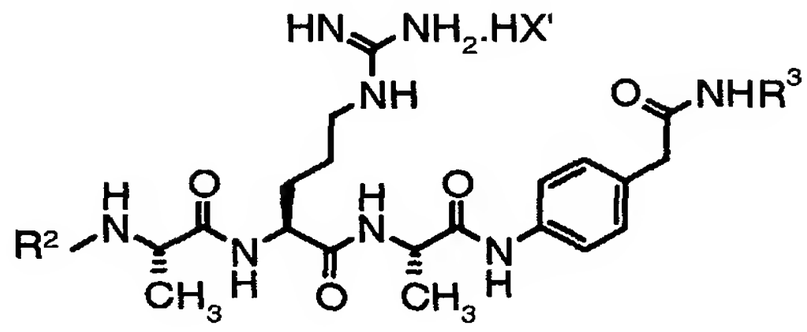
(i)

or a group of sub-formula (ii)



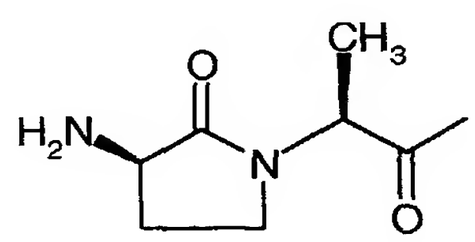
(ii)

with a compound of formula (III)



(III)

wherein X' is an anion, R^3 is hydrogen or a protecting group for an amino group of an acetamide, and R^2 is a group of sub-formula (iii)



(iii)

or hydrogen,

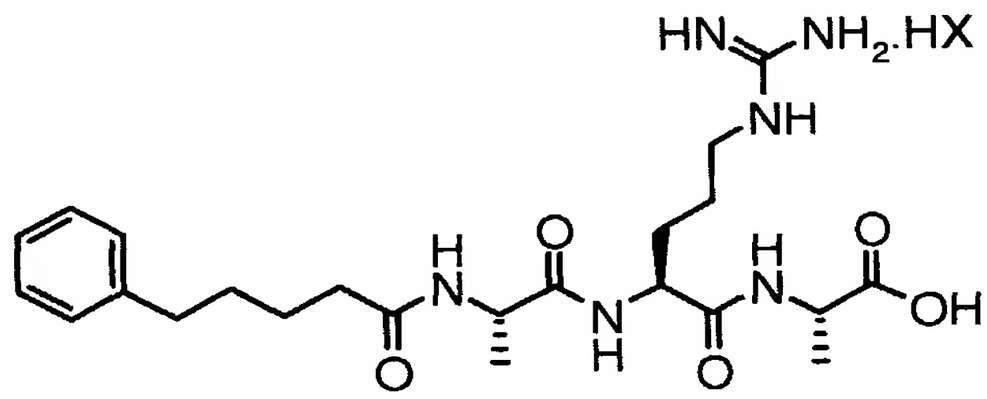
provided that when R^1 is a group of sub-formula (i), R^2 is a group of sub-formula (iii) and where R^1 is a group of sub-formula (ii), R^2 is hydrogen;

and thereafter if desired, converting the resultant acid addition salt to a different salt.

2. A process according to claim 1 wherein X and X' are halides.

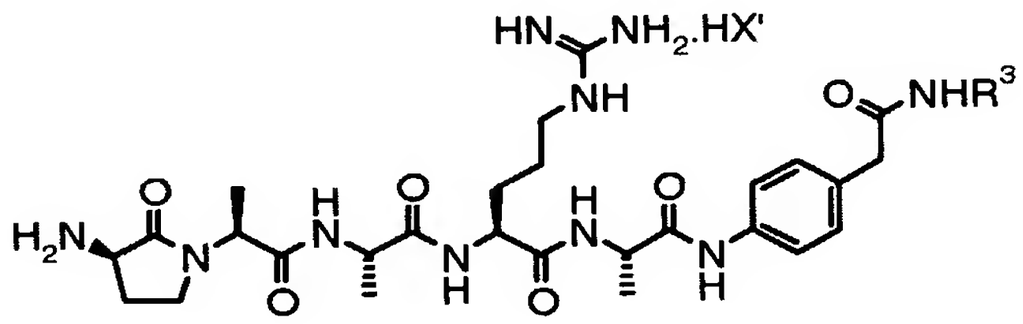
3. A process according to claim 1 or claim 2 wherein R^3 is hydrogen.

4. A process according to any one of the preceding claims which comprises coupling a carboxylic acid of the formula (IV) or a salt thereof,



(IV)

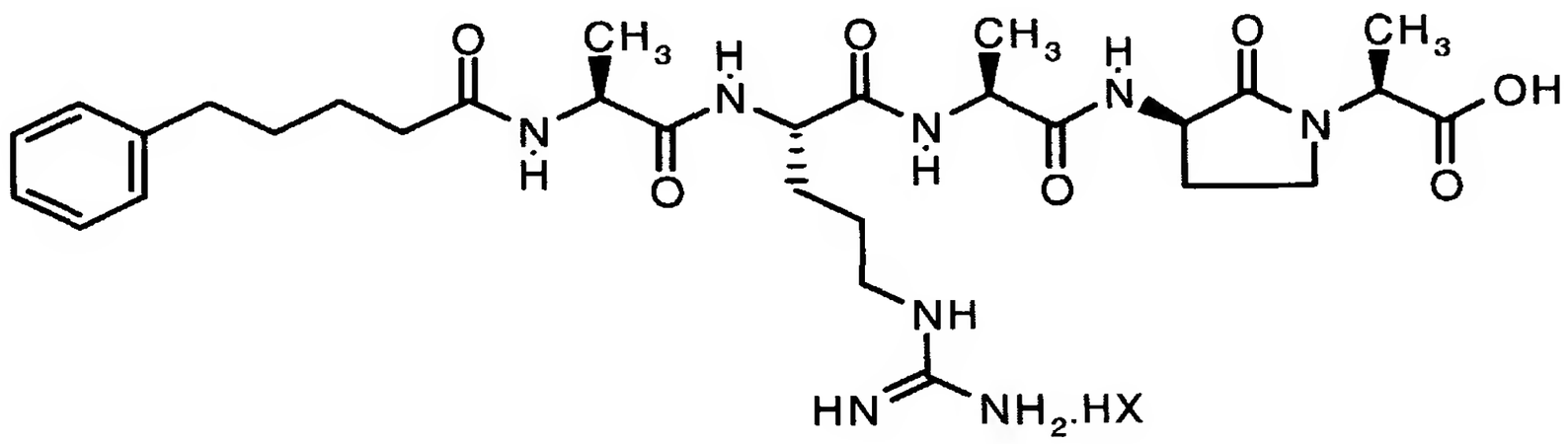
wherein X is as defined above, with an amine of the formula (V) or a salt thereof



(V)

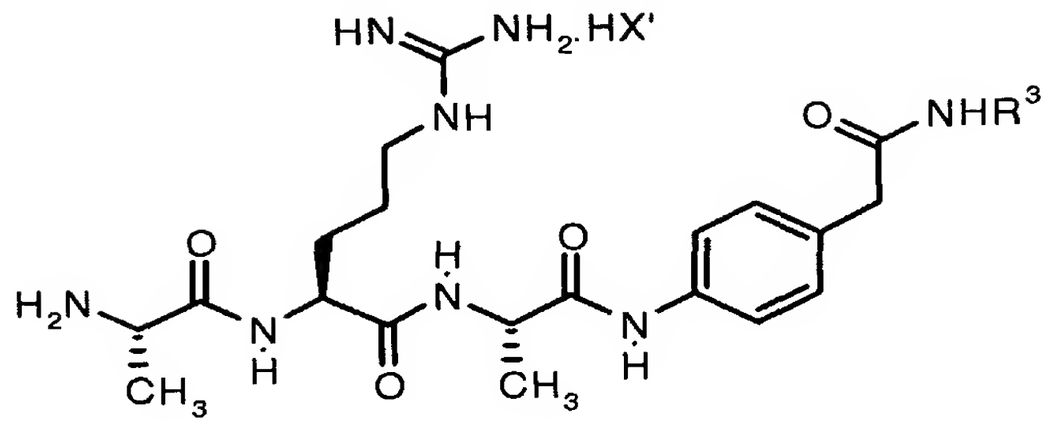
wherein X' and R^3 are as defined in claim 1.

6. A process according to any one of claims 1 to 4 which comprises coupling a carboxylic acid of the formula (VI) or a salt thereof,



(VI)

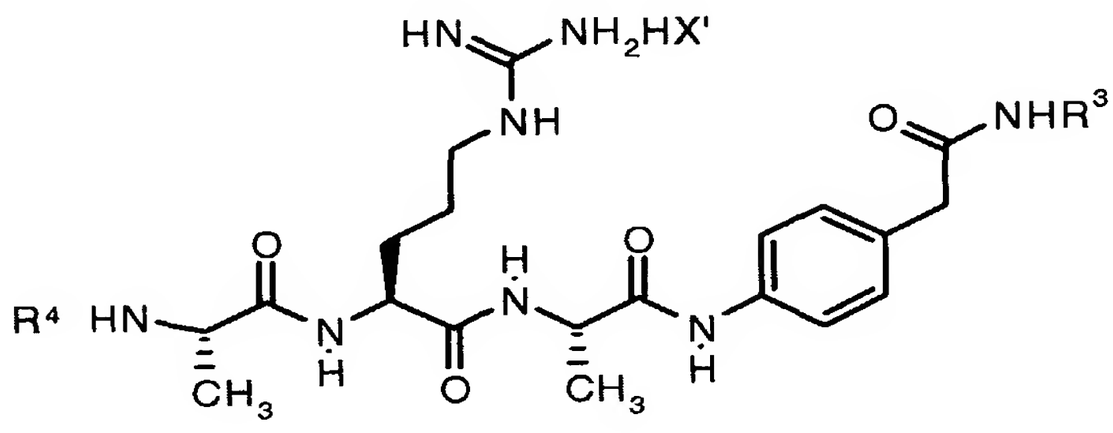
wherein X is as defined above with an amine of the formula (VII) or a salt thereof



(VII)

wherein X' and R^3 are as defined in claim 1.

7. A process according to claim 6 wherein the compound of formula (VII) is obtained by selectively removing protecting group R^4 from a compound of the formula (VIII)



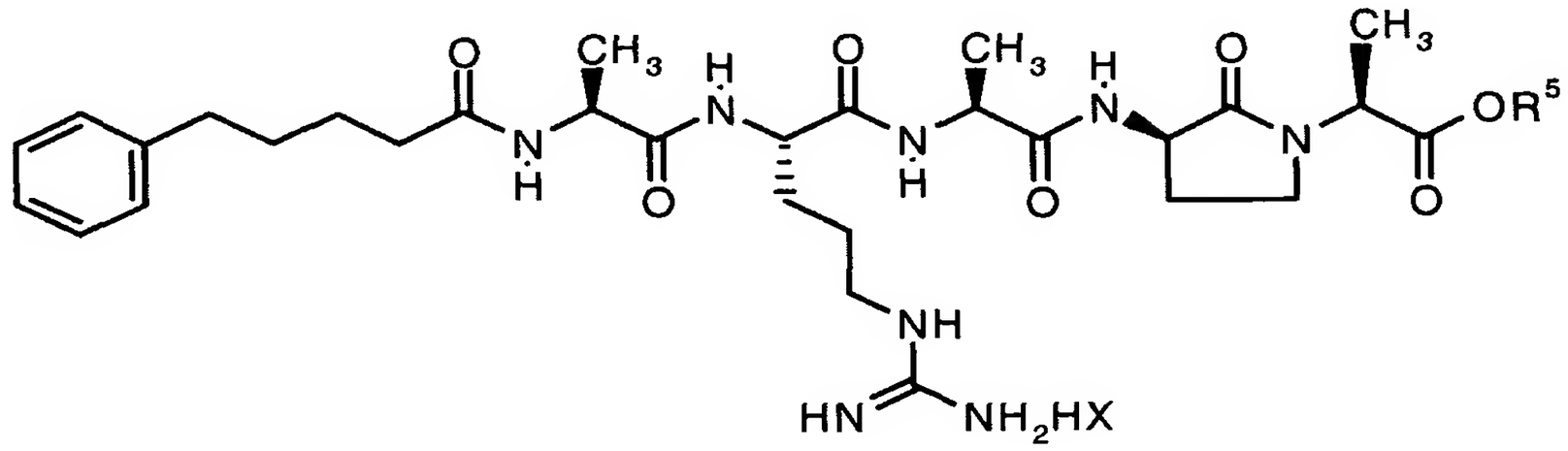
(VIII)

wherein X and R^3 are as defined in claim 1 and R^4 is an amino protecting group.

8. A process according to claim 7 wherein R^4 is benzyloxycarbonyl group.

9. A process according to claim 8 wherein the group R^4 is removed by catalytic hydrogenation.

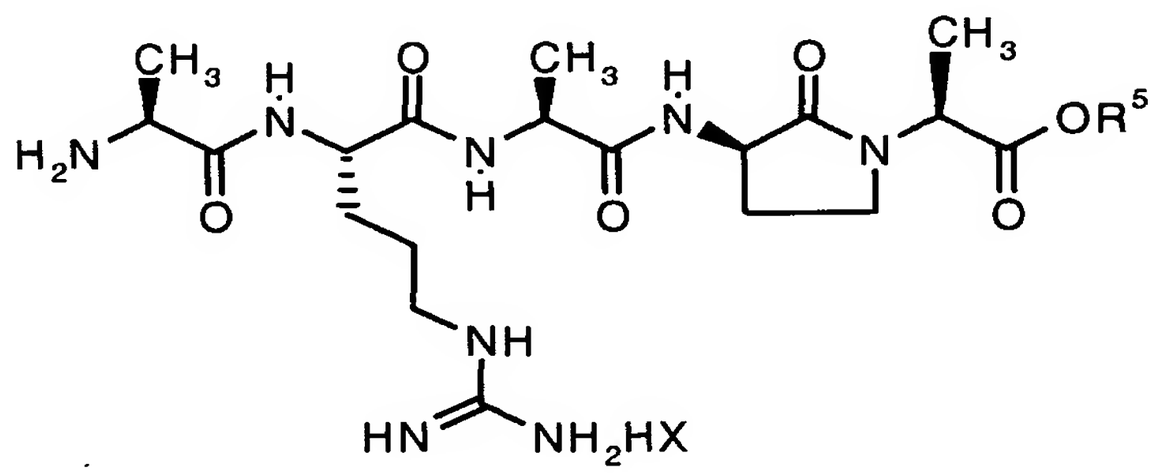
10. A process according to claim 6 wherein the compound of formula (VI) or a salt thereof is prepared by hydrolysis of an ester of formula (IX)



(IX)

wherein R^5 is alkyl or aralkyl and X is as defined in claim 1.

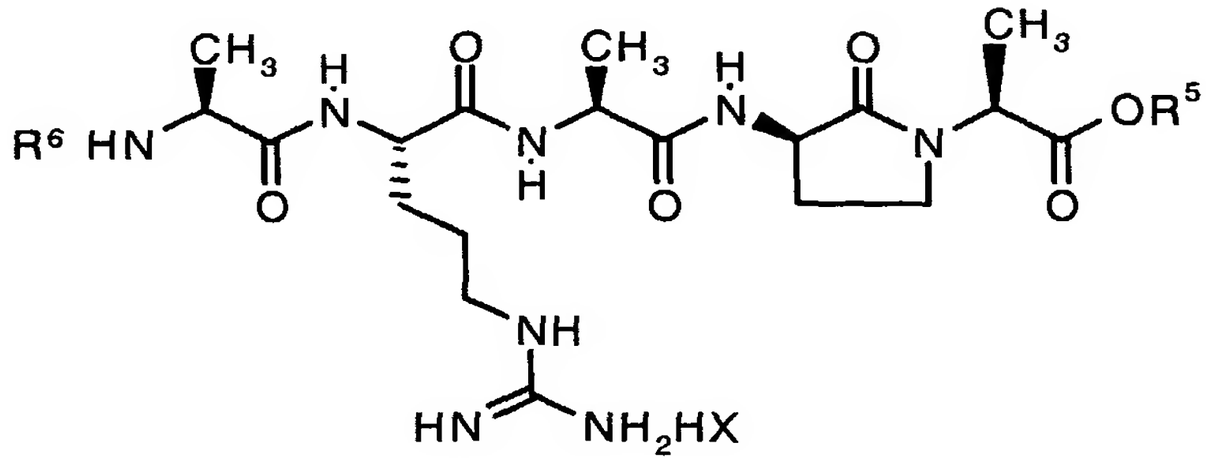
11. A process according to claim 10 wherein the compound of formula (IX) is obtained by coupling an amine of formula (X) or a salt thereof



(X)

wherein R^5 is as defined in claim 10 and X is as defined in claim 1 with 5-phenylvaleric acid.

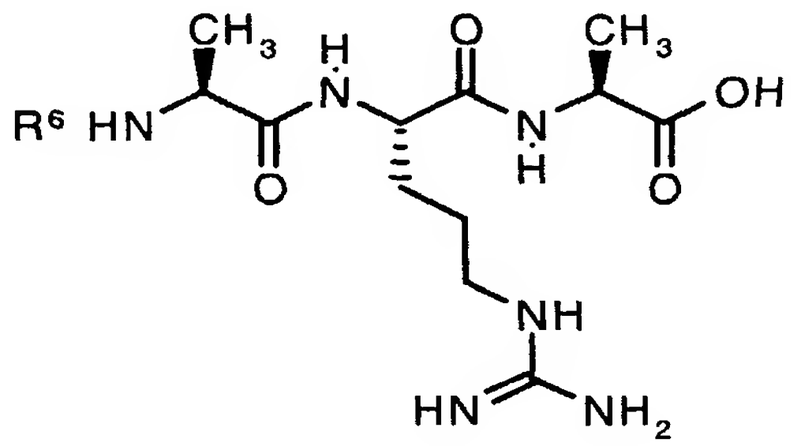
12. A process according to claim 11 wherein the compounds of formula (X) is prepared prepared by deprotection of a compound of formula (XI)



(XI)

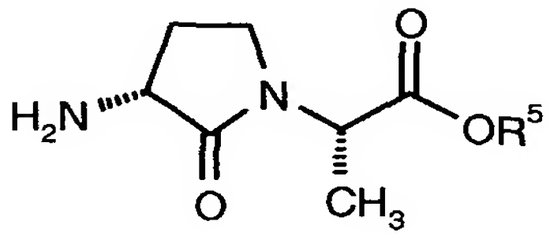
where R^5 is as defined in claim 10 and X is as defined in claim 1, and R^6 is an amine protecting group.

13. A process according to claim 12 where the compound of formula (XI) is prepared by coupling together a carboxylic acid of formula (XII) or a salt thereof



(XII)

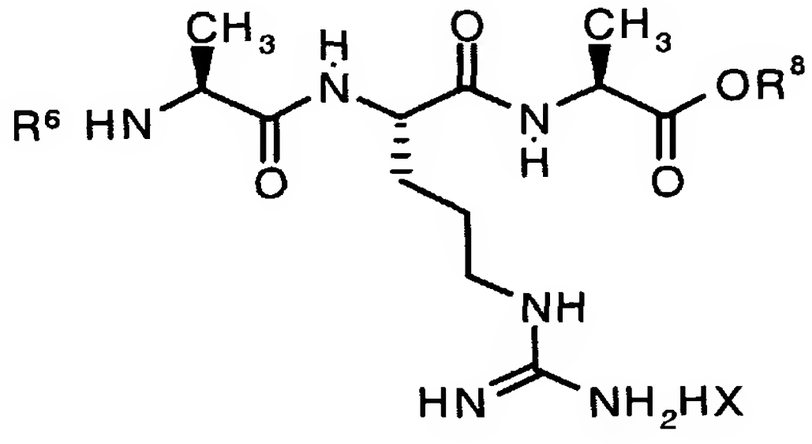
where R^6 is as defined in claim 12, with a compound of formula (XIII) or a salt thereof



(XIII)

wherein R^5 is as defined in claim 10.

14. A process according to claim 13 wherein the compound of formula (XII) is obtained by hydrolysis of an ester of formula (XVI)



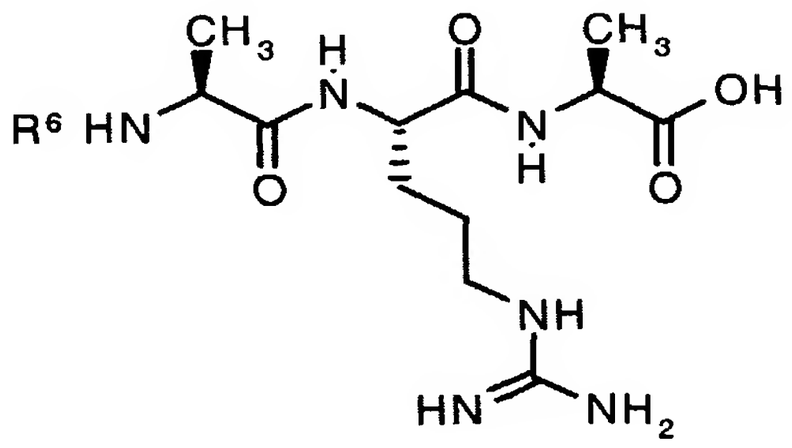
(XVI)

where R^6 is as defined in claim 12, X is as defined in claim 1 and R^8 is alkyl or aralkyl.

15. A compound of formula (X) as defined in 11.

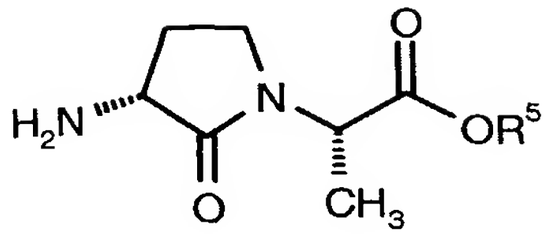
16. A compound of formula (XI) as defined in claim 12.

17. A method of preparing a compound according to claim 15 or claim 16 which comprises coupling together a carboxylic acid of formula (XII) or a salt thereof



(XII)

where R^6 is as defined in claim 12, with a compound of formula (XIII) or a salt thereof



(XIII)

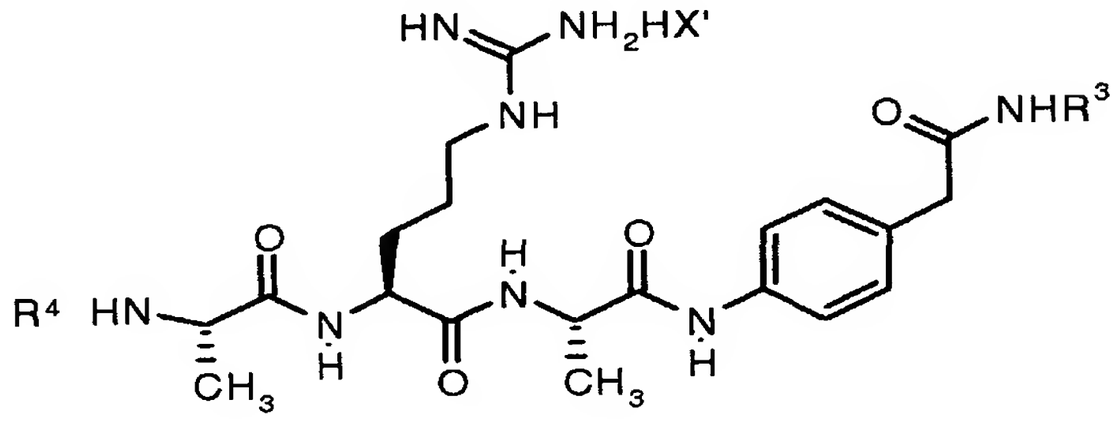
wherein R^5 is as defined in claim 10; and thereafter if desired, hydrolysing the ester of formula (XI) as defined in claim 12 thus obtained to an acid of formula (X) as defined in claim 11.

18. A compound of formula (IV) as defined in claim 4.

19. A compound of formula (V) as defined in claim 4.

20. A compound of formula (VII) as defined in claim 6.

21. A process for preparing a compound according to claim 20 which comprises selectively removing protecting group R^4 from a compound of the formula (VIII)

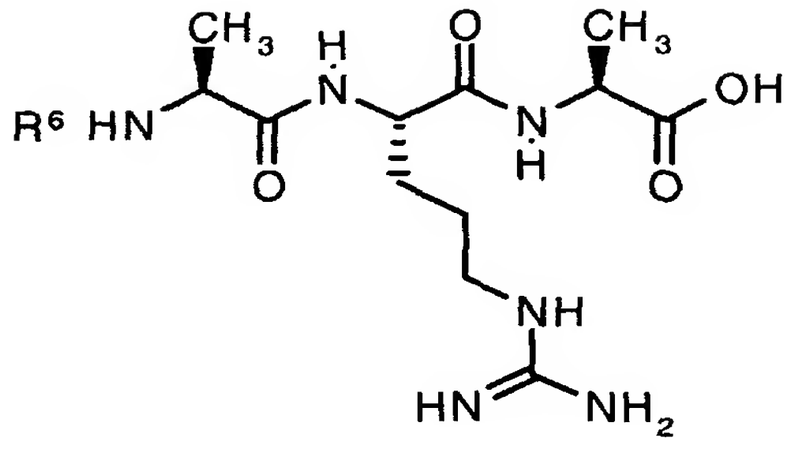


(VIII)

wherein X and R^3 are as defined in claim 1 and R^4 is an amino protecting group.

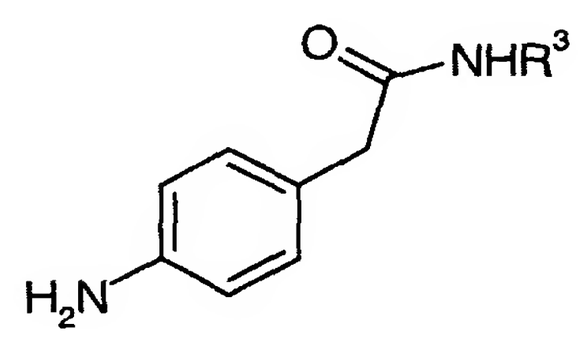
22. A compound of formula (VIII) as defined in claim 6.

23. A process for preparing a compound according to claim 22, which process comprises coupling a compound of formula (XII)



(XII)

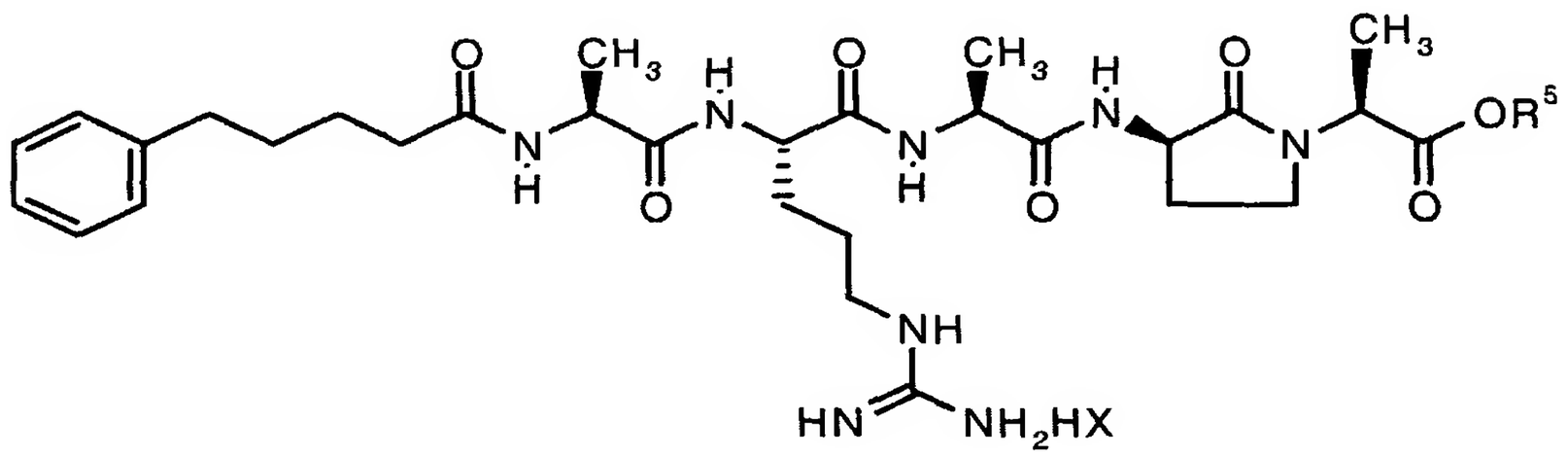
where R^6 is as defined in claim 12, is coupled with a compound of formula (XV)



(XV)

wherein R^3 is as defined above, and the isolating the product as the desired salt.

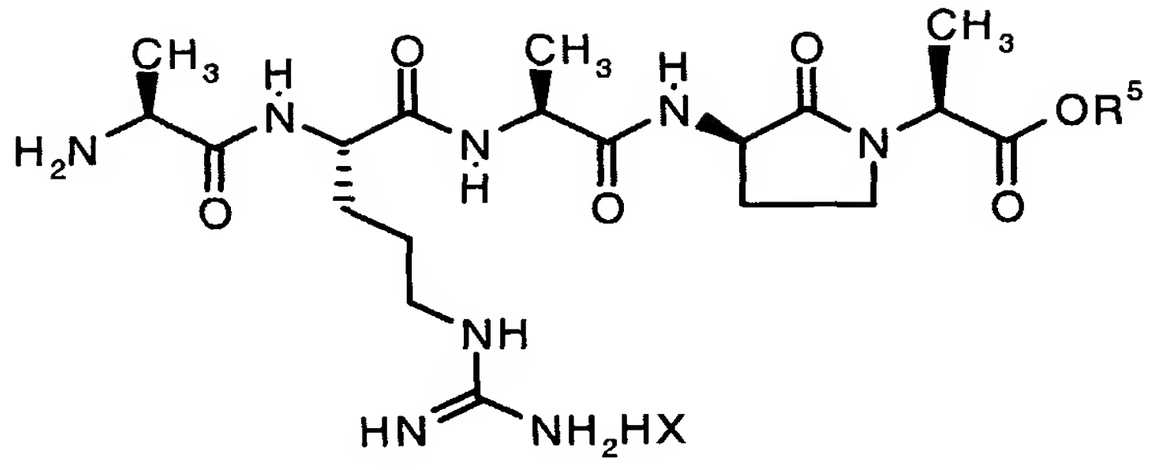
24. A compound of formula (IX)



(IX)

wherein R^5 is alkyl or aralkyl and X is as defined in claim 1.

25. A process for preparing a compound according to claim 24 which process comprises coupling an amine of formula (X) or a salt thereof

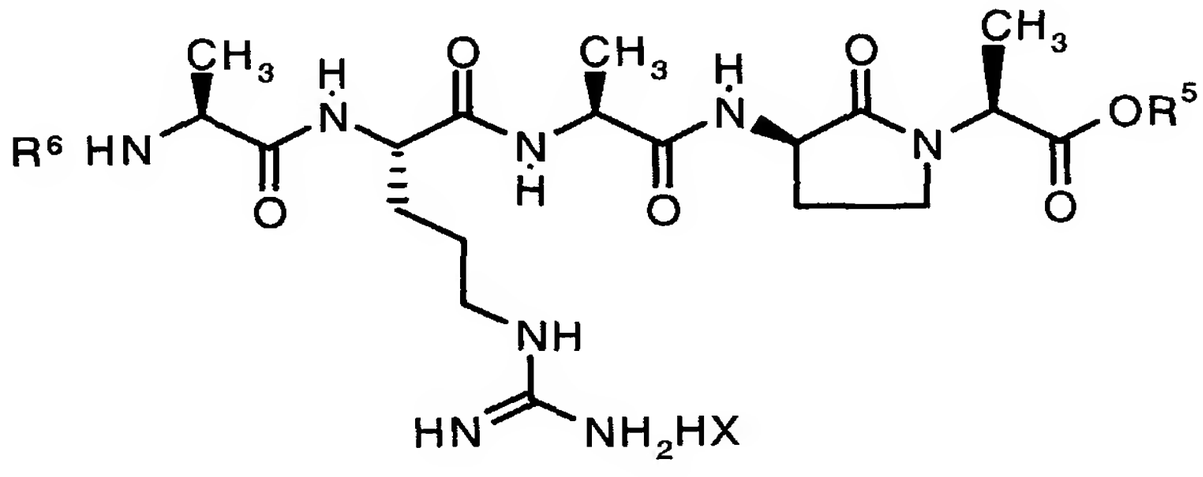


(X)

wherein R^5 is as defined in claim 10 and X is as defined in claim 1 with 5-phenylvaleric acid.

26. A compound of formula (X) as defined in claim 11.

27. A process for preparing a compound according to claim 26 which comprises deprotection of a compound of formula (XI)

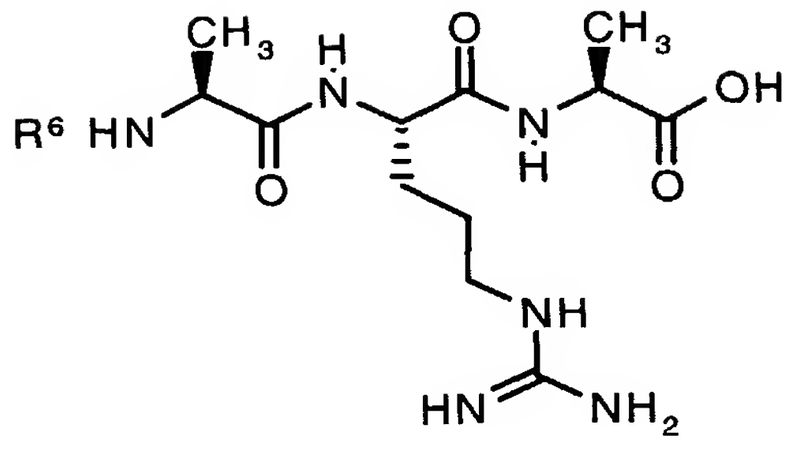


(XI)

wherein R^5 is as defined in claim 10 and X is as defined in claim 1, and R^6 is an amine protecting group.

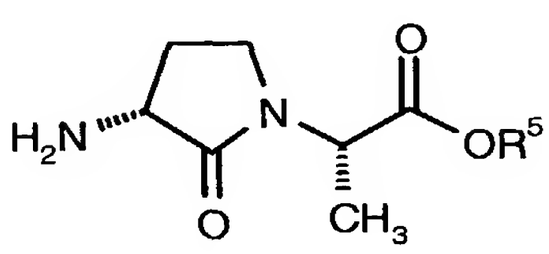
28. A compound of formula (XI) as defined in claim 12.

29. A process for preparing a compound according to claim 28 which comprises coupling together a carboxylic acid of formula (XII) or a salt thereof



(XII)

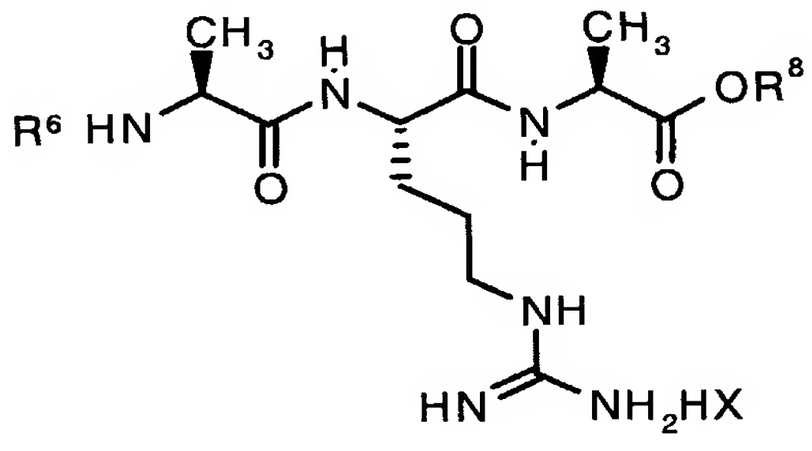
where R^6 is as defined in claim 12, with a compound of formula (XIII) or a salt thereof



(XIII)

wherein R^5 is as defined in claim 10.

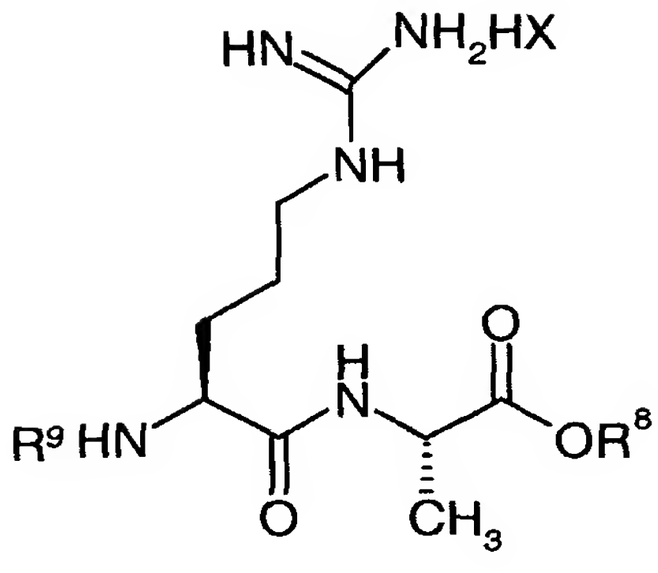
30. A compound of formula (XVI)



(XVI)

wherein R^6 is as defined in claim 12, X is as defined in claim 1 and R^8 is alkyl or aralkyl.

31. A process for preparing a compound according to claim 30 which process comprises selective removal of a protecting group R^9 from a compound of formula (XVII),

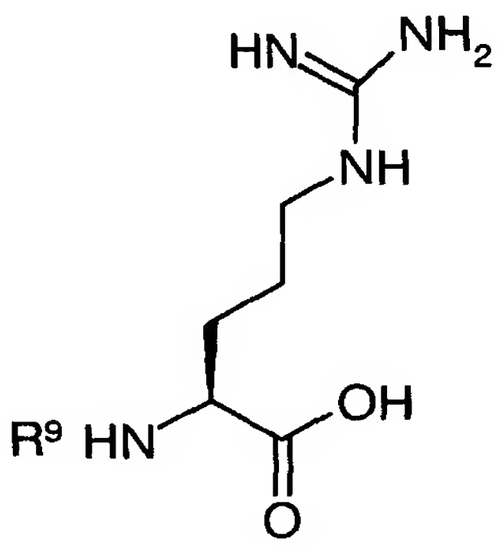


(XVII)

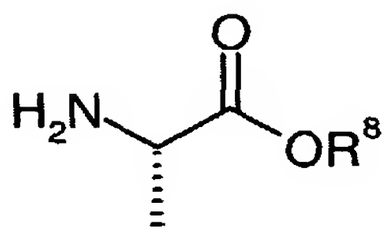
wherein X is as defined in claim 1, R^8 is as defined in claim 30 and R^9 is an amino protecting group which can be selectively removed in the presence of X and R^8, and coupling the product with a R^6 protected (S)-alanine.

32. A compound of formula (XVII) as defined in claim 31.

33. A process for preparing a compound according to claim 32 which comprises coupling a compound of the formula (XVIII) or a salt thereof, and a compound of the formula (XIX) or a salt thereof:



(XVIII)



(XIX)

wherein R^8 and R^9 are as hereinbefore defined, in the presence of a suitable acid of formula HX, so as to give a protonated product.

INTERNATIONAL SEARCH REPORT

Intern Application No
PCT/GB 02/05741

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/47 C07K14/705 C07K5/08 C07K5/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	FR 2 597 107 A (ELLEM INDUSTRIA FARMACEUTICA) 16 October 1987 (1987-10-16) page 4 ---	32,33

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
29 April 2003	15/05/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Masturzo, P

INTERNATIONAL SEARCH REPORT

Interna Application No
PCT/GB 02/05741

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	Y SASAKI ET AL.: "Studies on analgesic oligopeptides II. Structure-activity relationship among thirty anlogs of a cyclic dipeptide, cyclo (Tyr-Arg)" CHEMICAL AND PHARMACEUTICAL BULLETIN., vol. 30, no. 12, 1982, pages 4435-4443, XP002239766 PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO., JP ISSN: 0009-2363 see page 4437, Table II, Vth compound ---	32,33
X	V SCHELLENBERGER ET AL.: "Papainkatalysierte kinetisch kontrollierte Peptidsynthese. Verwendung von Alkylestern des Arginins als Aminokomponente" MONATSHEFTE FUR CHEMIE., vol. 120, 1989, pages 437-443, XP002239767 SPRINGER VERLAG. WIEN., AT ISSN: 0026-9247 table 1 ---	32,33
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INTERNATIONAL SEARCH REPORT

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